Ontario

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ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

KAUFFMAN

Hearing held
8th floor
180 Dundas Street West
Toronto, Ontario

In Ch. Etc.

The Honourable Mr. Justice S.G.M. Grange	Commissioner
P.S.A. Lamek, Q.C.	Counsel
E.A. Cronk	Associate Counsel
Thomas Millar	Administrator

Transcript of evidence
for

November 28, 1983

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ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

Hearing held on the 8th Floor, 180 Dundas Street West, Toronto, Ontario, on Monday, the 28th day of November, 1983.

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THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner

THOMAS MILLAR - Administrator

MURRAY R. ELLIOT - Registrar

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APPEARANCES:

P.S.A. LAMEK, Q.C.) E. CRONK)	Commission Counsel
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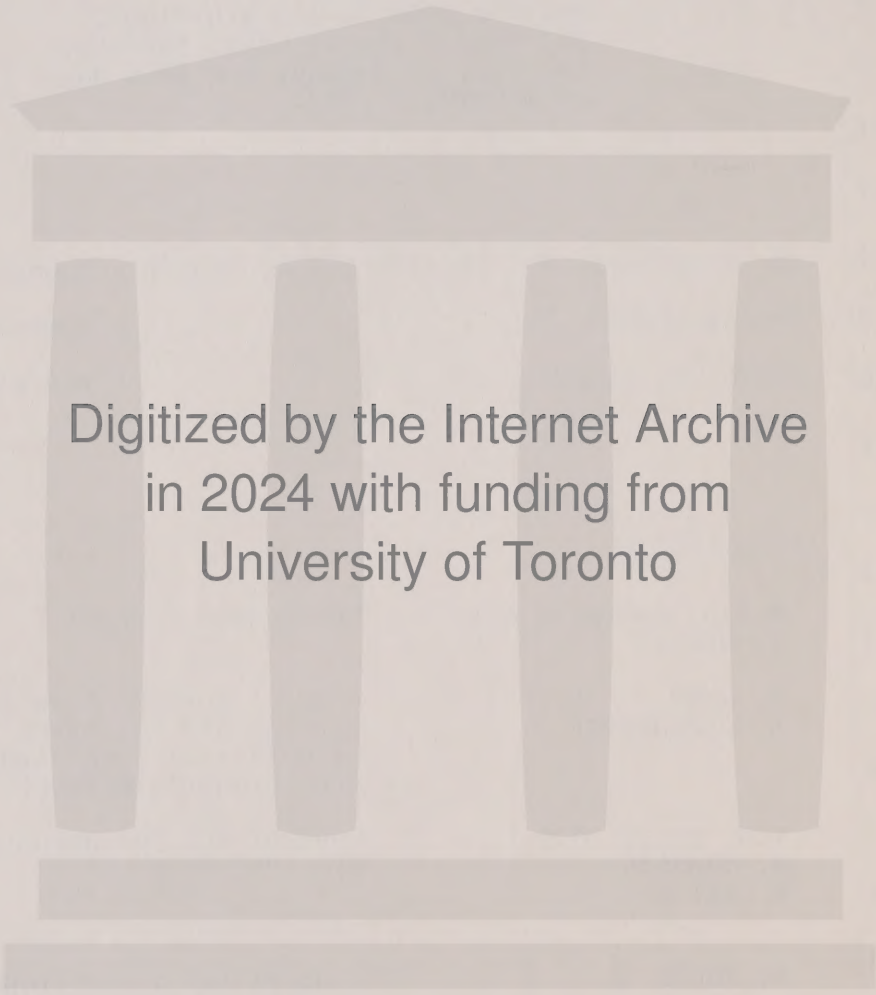
I.G. SCOTT, Q.C.) M. THOMSON) R. BATTY)	Counsel for The Hospital for Sick Children
D. YOUNG	Counsel for The Metropolitan Toronto Police
W.N. ORTVED	Counsel for numerous Doctors at The Hospital for Sick Children
B. SYMES	Counsel for the Registered Nurses' Association of Ontario and 35 Registered Nurses at The Hospital for Sick Children

(Cont'd)



APPEARANCES: (Continued)

D. BROWN	Counsel for Susan Nelles - Nurse
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J.A. OLAH	Counsel for Janet Brownless - R.N.A.
B. JACKMAN	Counsel for Mrs. M. Christie - R.N.A.
F.J. SHANAHAN	Counsel for Mr. & Mrs. Dominic Lombardo (parents of deceased child Stephanie Lombardo); and Heather Dawson (mother of deceased child Amber Dawson)
W.W. TOBIAS	Counsel for Mr. & Mrs. Hines (parents of deceased child Jordan Hines)
J. SHINEHOFT	Counsel for Lorie Pacsai and Kevin Garnet (parents of deceased child Kevin Pacsai)

VOLUME 70

E R R A T A

Volume 69 - Thursday, November 24, 1983

Page 5133, line 10 - "naloxone" should be "digoxin"

Page 5375, line 3 - "impossible" should be "possible"

Page 5377, line 11 - "just in Cook" should be "Justin Cook"

Page 5408, line 20 - "more" should be "four"

INDEX OF WITNESSES

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AA/BM/ak

---Upon commencing at 2:00 p.m.

THE COMMISSIONER: Yes, Miss Cronk.

MS. CRONK: Good afternoon, sir. Our next witness is Dr. Ralph Kauffman. I call Dr. Kauffman.

DR. RALPH KAUFFMAN, Sworn

DIRECT EXAMINATION BY MS. CRONK:

Q. Thank you. Dr. Kauffman, as I understood it, you obtained your medical degree at the University of Kansas in Kansas City in 1965, is that correct, sir?

A. That is correct.

Q. You spent the following year as an intern at Kansas City General Hospital in the same City?

A. That is correct.

Q. From 1966 to 1968, Doctor, as I understand it, you served as a surgeon with the United States Public Health Service and were detailed to the Food and Drug Administration with the Bureau of Medicine. Do I have that correctly?

A. That is correct.

Q. In 1968 you commenced a residency in Pediatrics at the University of Kansas Medicine Centre again in Kansas City?

A. That is correct.

Q. And your post-doctoral training, Doctor, was completed, as I understand it, at the same University and Medical Centre in 1972 in the area of Clinical Pharmacology?

A. That is right.

Q. Doctor, you have served as well and held a number of teaching positions at a variety of universities. In the years 1976 to 1979, for example, it is my information that you served as an Associate Professor of Pediatrics and of Pharmacology at the University of Kansas?

A. That is correct.

Q. And during the same period, Doctor, you served as Vice-Chairman of the Department of Pediatrics at the same University?

A. That is right.

Q. Prior to that, as I understand it, you taught Pediatrics at the University of Missouri?

A. I was an adjunct professor there.

Q. All right. And in 1979, Doctor, you left Kansas City and accepted a position as an Associate Professor of Pediatrics and of

Pharmacology at Wayne State University School of Medicine in Detroit, Michigan?

A. That is correct.

Q. And in 1979 you became an Associate Attending Physician at Children's Hospital in Michigan?

A. That is correct also.

Q. The following year you became a full attending physician at the same hospital?

A. That's right.

Q. And in 1982, Doctor, as I understand it, you became a Professor of Pediatrics at Wayne State University School of Medicine in Detroit, a position which you continue to hold today?

A. That's right.

Q. And as well, Doctor, you became - I'm sorry, you became in 1982 and are today the Director of the Division of Clinical Pharmacoloy and Toxicology at Children's Hospital of Michigan in Detroit?

A. That is right.

Q. Doctor, you have been kind enough to provide to me a copy of your curriculum vitae and it details any number of memberships which you have had or continue to have in a variety of

professional groups and associations. You are, for example, as I understand it, currently the Chairman of the Pharmacy and Therapeutics Committee at your hospital, Children's Hospital in Michigan?

A. That is right.

Q. And you are a member of the Pediatric Chairman's Senior Advisory Committee at Wayne State University?

A. That is right.

Q. And you are a member of the Executive Committee of the American Academy of Pediatrics Section on Clinical Pharmacology and Therapeutics?

A. I was a member; I went off that Committee last year but I was a member for four years I believe.

Q. And in fact you previously served, as I understand it, as Chairman of that Section, did you not?

A. That is correct.

Q. Doctor, you are the author or co-author of a great number of book chapters, academic papers, abstracts and articles, all of which are detailed in your curriculum vitae. I would ask you to identify it as I have described it.

A. It is correct as submitted.

MS. CRONK: Thank you, sir.

THE COMMISSIONER: What number are we at?

THE REGISTRAR: 265.

THE COMMISSIONER: Exhibit 265.

---EXHIBIT NO. 265: Curriculum Vitae of Dr. Ralph Kauffman.

MS. CRONK: Thank you, sir.

THE COMMISSIONER: Before you forget, Miss Cronk, we discussed the timing question. We don't know what's going to happen this week but we started late. We thought we would sit until 5 o'clock tonight and perhaps even sit late tomorrow just to make sure that - Doctor, I use these terms, I don't mean to be offensive - but just to make sure we dispose of you before the end of the week.

THE WITNESS: I would appreciate this, thank you.

THE COMMISSIONER: Yes, all right. Yes, Miss Cronk.

MS. CRONK: Thank you, sir.

Q. Dr. Kauffman, I don't propose to detail with any particularity the numerous articles and abstracts that you have written over the years

but would it be fair to suggest that you have written extensively in the areas of clinical pharmacology and pharmacokinetics of a variety of drugs?

A. Yes, that is correct.

Q. You have written as well, as I understand it, Doctor, on such topics as appropriate drug dosages for children?

A. That is correct.

Q. And the clinical interpretation and application of drug concentration data?

A. Yes, that is correct.

Q. And as well, Doctor, the analysis of various drugs using high performance liquid chromatography or, as has been described in these proceedings, HPLC?

A. That is correct.

Q. And as well, Doctor, on the use of the drug naloxone in newborns?

A. That is correct.

Q. Doctor, do I take it that in the course of your medical and pharmacological training, as well as in your professional endeavours in teaching you have had occasion to become familiar with the drug digoxin?

A. That is correct.

Q. Would it be fair to suggest, Doctor, having regard to the contents of your curriculum vitae, that prior to the summer of 1982 that drug was not a drug of particular research interest to you?

A. That is correct, it was never a drug of direct research interest. I was familiar with it because of clinical use and also within the context of teaching pharmacology, and the general information anybody working in that area would have.

Q. Is the drug in fact used for therapeutic purposes in your own hospital, Doctor?

A. Yes, it is.

Q. And is your hospital, Doctor, as the name suggests, restricted to the treatment and care of children?

A. That is correct.

Q. What age range of children, Doctor, are cared for normally in your hospital?

A. Generally from birth to 18 years.

Q. All right. Doctor, following the summer of 1982, as I understand it, digoxin has been a drug that has attracted something more of your particular interest. Do I have that correctly?

A. Yes, I'm afraid so.

Q. Doctor, as I understand it, you first became involved in the matters that concern this Commission in late to mid-August of 1982 when you were contacted, I believe by Mr. Jerome Wiley of the Crown Attorney's Offices here in Toronto Do I have that correctly, sir?

A. Yes, that is correct.

Q. And he spoke to you, as I understand it, to determine if you would be willing to act as a consultant?

A. That's right.

Q. All right. Doctor, can you outline for us, if you would, please, what services specifically were requested of you at that time?

A. At the time he initially contacted me, my understanding was that he wanted me to serve as a consultant on an ad hoc basis to look at the general issues pertaining to the involvement of digoxin in the cases that they were investigating at that time.

At that time, the time that he originally called me, nothing more specific than that was discussed. Following a meeting with him at a later date, and I don't recall specifically now without looking it up, but within a month or two

after that, then specific questions were addressed to me and I was asked to review a number of cases that were currently being investigated to try to help them assess what role if any digoxin might have played in the death of the infants they were investigating.

Q. All right. Doctor, just stopping there for a moment then. As I understood what you have just said, the original request was to provide, as you have said, from time to time or on an ad hoc basis, pharmacological advice. Do I have that correctly?

A. Yes, that is correct.

Q. And subsequently you were asked to undertake a specific review of specific cases?

A. That is right.

Q. All right. And for the purposes you understood it of assessing, I believe you said the likelihood of involvement of digoxin in those cases.

A. That's right.

Q. All right. And was it your understanding, Doctor, that the cases that you were being asked to review were those of children who had

died at the Hospital for Sick Children during the period July, 1980 through to March 22nd, 1981?

A. I believe that is correct, yes.

Q. Were you asked, Doctor, at that time, to prepare a report in writing of any kind with respect to that review?

A. Yes, I was eventually asked to produce a written report to detail my findings following my review of the specific cases.

Q. All right. Doctor, may I ask you, at the time that you were requested to undertake that review, were you familiar in any detail with the pharmacokinetics of digoxin, that is, the movement and distribution of the drugs throughout the body following administration?

A. Yes, I was familiar with it, I had lectured on it for medical students and house staff. So, I was familiar with it.

Q. All right. Did you, Doctor, as well as a result of the request to undertake this review, conduct any kind of a literature review to expand your knowledge of digoxin in that area?

A. Yes, I did. I accumulated a great deal more literature from various sources, primarily reprints from published papers, particularly

I had to do additional literature research in the area of poisoning and post mortem digoxin measurements because that was an area which had not previously been of a particular interest to me.

Q. Doctor, as part of that literature review, I take it you were interested then to expand your familiarity or knowledge as to both the therapeutic and the toxic levels of the drug that might result in blood and tissue following administration?

A. Yes, that is correct.

Q. Were you concerned as well, Doctor, to expand your knowledge concerning the elimination of this drug from the body?

A. Please state that again.

Q. I'm sorry, Doctor. Were you concerned as well to expand your knowledge as to the rate of elimination, if you will, of this drug from the body?

A. Yes, that was part of my over-all review, certainly.

Q. And did you address as well, Doctor, the reported literature concerning the interpretation of digoxin level data both from ante mortem and post mortem specimens?

A. Yes, I did.

Q. Were you provided, Doctor, by Mr. Wiley or by anyone else with written terms of reference or specific requests in writing as to the scope of the review that you were being asked to undertake?

A. The scope of the review as I recall it was communicated to me primarily verbally but I was submitted specific questions to which they wanted me to respond within my written report. I was not restricted to those written questions but they were to be included.

BB
EMT/cr

Q. Aside from those specific questions, and I'll come back to that in a moment, Doctor, did you receive in writing from Mr. Wiley or anyone else confirmation as to the nature and the purpose of the review that was being asked of you?

A. I have the letter confirming - I probably should refer to that before I answer you. I am not sure how specific it was.

Q. Please do. Please feel free to do so.

A. I will look and see if I have any specific correspondence at hand that I can... which will help give me more precise answers.

Q. Thank you, Doctor.

The question, Doctor, that I am most interested in, to assist you, is to whether or not what might be described as terms of reference for this review were outlined for you in writing at any time?

A. No, not specifically. As I recall the letter that I am thinking of simply confirmed, and I can't put my hands on it right now, simply confirmed that I would be providing consultation to them and submitting a written report at some point in future but I was not restricted in

any way to any particular points of reference other than, as I recall, other than the specific questions that was provided to me that they wanted specifically addressed.

Q. Perhaps, Doctor, in due course if you could turn up that letter we would be interested in seeing it.

A. Yes.

Q. But for the moment, Doctor, as I understand it you did ultimately deliver two written reporting letters to Mr. Wiley with respect to the review that you had undertaken. Do I have that correctly?

A. That is correct.

Q. Doctor, I am showing to you a bound version of two letters, one of which is dated I believe December 16th, 1982, and it is some 15 pages in length. It purports to be over your signature. And the second letter, some four pages in length, dated January 17th, 1983. Are these the reporting letters which were ultimately delivered to Mr. Wiley concerning the review that you had conducted?

A. Yes, they are.

Q. Do you have a copy of those

letters with you, Doctor?

A. Yes, I have another copy here.

THE COMMISSIONER: Shall we make them A and B?

MS. CRONK: I would suggest labelling as one, Mr. Commissioner.

THE COMMISSIONER: All in one. Exhibit 266, is it?

---EXHIBIT NO. 266: 15-page letter dated December 16, 1982 and four-page letter dated January 17th, 1983, from Dr. Kauffman.

MS. CRONK: Q. Doctor, you have referred as well to certain specific questions that were provided to you for a response.

I direct you to page 13 through 15 of the first reporting letter if you would, please.

THE COMMISSIONER: The pages again?

MS. CRONK: I am sorry, pages 13 through 15 of the first reporting letter. Once again we have a numbering problem, Mr. Commissioner. There is a larger set of numbers on the far right-hand side. I am referring to the number on the letter itself.

Q. Do you have that, Dr. Kauffman.

A. Yes, I have.

THE COMMISSIONER: Well, there is no

way we can conceal the number of pages in the police report.

MS. CRONK: Well, it appears that they are mounting, sir, judging from the numbers on this page. But you are quite right it is contained in the police report.

THE COMMISSIONER: Everybody will know when to ask for pages 160 to 186 inclusive.

MS. CRONK: Q. Doctor, the three pages starting at page 13 as I take them appear to be addressing, in response if you will, certain specific questions that were posed of you.

Are these the answers to the questions that you referred to a few moments ago?

A. Yes, responses to the written questions I had received.

Q. All right. And, Doctor, I am showing to you as well a one-page document entitled "Questions for Dr. Kauffman" and I would ask you whether this is a typewritten version of the questions that were presented to you?

A. Yes. It looks like the list of questions I received.

MS. CRONK: Mr. Commissioner, I would ask that that be marked as the next exhibit.

THE COMMISSIONER: Exhibit 267.

---EXHIBIT NO. 267: Document entitled "Questions for Dr. Kauffman".

MS. CRONK: Q. Dr. Kauffman, who did you understand had retained your services for the purposes of this review?

A. It was my understanding it was Mr. Jerry Wiley, Jerome Wiley.

Q. From whom, Doctor, did you receive this list of questions or do you recall?

A. It was from his staff. I don't remember the specific individual but it was from either him or his staff. I think it was handed to me when I was in Toronto as I recall, and not mailed to me. My recollection is it was given to me when I was here on one occasion.

Q. And, Doctor, perhaps it is obvious but inasmuch as the end of your first reporting letter addresses specifically these questions I gather they were delivered to you some time in advance of the completion by you of your review of these cases?

A. That is correct.

Q. Doctor, apart from the literature review which you told us you undertook in

order to perform this review can you help me as to what information was made available to you concerning these children in order to assist you in conducting your review?

A. I had summaries of the cases which I understood had been prepared by Dr. Hastreiter.

I had the digoxin measurement data from the Centre for Forensic Studies. I had digoxin data from the Hospital for Sick Children. I had summaries, various summaries that had been prepared of that data, tabulations, simply for convenience.

I had available to me all the laboratory data sheets from the patients' charts of the patients I was to review, and then I had the opportunity to review copies of the actual charts on one occasion prior to submitting my report.

Q. Did you in fact, Doctor, review all 36 medical records?

A. Yes, I did eventually look at 36 charts, as I recall it, 36 records.

MS. CRONK: Mr. Registrar, would you please show Dr. Kauffman Exhibit 264.

Doctor, Exhibit 264 in these proceedings is a bound volume of what we understand to be Dr. Hastreiter's case summaries with respect to these

36 children.

I ask you to look at it and if you would could you tell us whether or not those are the case summaries that were provided to you for review?

A. There appears to be a page missing here.

Q. That is possible in the photo-copying, Doctor.

A. Yes.

Q. Although you will note the pages are numbered consecutively.

A. Yes.

Q. One through ... Do those appear to be the case summaries,Doctor, that you received?

A. Yes. Yes they do. Mine were arranged in a little different sequence. That is why I was hesitating. They look to be the same information that I had in summary form.

Q. Thank you, Doctor.

Doctor, you have told us as well that you had available to you various toxicological data if I can describe it as such from the Centre of Forensic Sciences.

To assist you, Doctor, there have been

a number of written reports prepared by Mr. Cimbura filed in these proceedings. The first is as Exhibit 95A through F.

First is a report dated January 11, 1982. Was a copy of the report provided to you?

A. I believe so. I can tell you exactly which reports I had.

- - - -

DM.jc
CC

What was the date?

Q. January the 11th, 1982, Doctor.

A. Yes, I have that one.

Q. And did you as well receive, Doctor, a copy of the report from Mr. Cimbura dated February 2nd, 1982?

A. Yes.

Q. And the third one, Doctor, that we have been provided with is a report dated March 25, 1982.

A. I have that report.

Q. Do you have that one?

A. Yes.

Q. The next is one dated April 6th, 1982.

A. That is correct.

Q. And next is one dated September 29th, 1982.

A. I did not have a copy of that.

Q. And the final one, Doctor, in the series is a report dated December the 31st, 1982, do you have a copy of that?

A. No, I did not have a copy of that report either.

Q. Other than the four written

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reports which were provided to you from Mr. Cimbura, were any further particulars concerning his toxicology assay results provided to you other than in the format of a written report?

A. Yes, I had some additional tabulated values on Patient Bilodeau, Belanger, Gionas, Gage, Woodcock, Inwood, Gage, Perreault, Floryn and Volk which were tabulated in a different form that came from the Centre of Forensic Studies but they were not a part of the formal report as I have had on the other cases.

Q. Thank you, Doctor, we will come to the specifics of that information in due course. You have told us as well, Doctor, that you had available to you the digoxin assay data from The Hospital for Sick Children; and would I be correct in assuming that you as well had access to and saw the autopsy reports and autopsy particulars on these children if those reports were contained in the medical record at the time that you reviewed them?

A. If they were in the medical record at the time they reviewed them a year ago I would have seen them, yes.

Q. And Doctor, this Commission has heard evidence from Dr. Harry Bain of The Hospital

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for Sick Children concerning a report which he prepared in June of 1982 concerning these deaths, an assessment of the deaths that had taken place during this time frame. Did you receive a copy of that report at the time that you were undertaking your review?

A. Yes, I did.

Q. As well, Doctor, we have heard evidence that there were and are maintained on the cardiology wards at The Hospital for Sick Children for the aid of the attending staff cardiologists packages known as zebra packages containing certain information with respect to the patients on that ward. Were you provided with any zebra package with respect to any of these children whose case you reviewed?

A. No, I don't recall seeing anything like that.

Q. Doctor, at the time you were asked to and agreed to undertake this review, a preliminary hearing which had been held in respect of certain charges against a nurse from The Hospital for Sick Children by the name of Susan Nelles had been completed, the preliminary hearing was complete and Nurse Nelles was discharged in May of 1982. Were you provided any information with respect to the preliminary hearing?

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A. I was provided what I think, as I recall it, was a summary of the hearing or whatever you call it, the Basis for Judgment or whatever, it was a summary of the hearing.

Q. There were in that case, Doctor, Reasons for Judgment delivered by his Honour Judge Vanek with respect to his decision?

A. That was it.

Q. Is that the document that you are referring to?

A. Yes, I believe so.

THE COMMISSIONER: I must have misunderstood it. Could we find out as close as we can when you were approached by Mr. Wiley?

THE WITNESS: As I recall it was during August of 1982, I don't recall the exact date or have any note of the exact date, but I think it was some time in August of 1982.

MS. CRONK: Q. I take it, Doctor, that is when you were approached originally to provide consulting services?

A. Right.

Q. Do you recall, Doctor, when you were requested to specifically undertake a review of these cases?

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A. I don't recall specifically because the events are rather blurred in my mind over the next few months, but probably it was within the next several months, during the next several months after that.

Q. Thank you, Doctor. Doctor, can you tell us as well, were you provided with a copy of any of the transcripts of evidence from the preliminary hearing that I have just described?

A. No, I didn't look at the transcripts of evidence.

Q. Doctor, you have told us that you did have available to you a copy of Dr. Bain's report with respect to these deaths. Did you discuss any of the cases which you were reviewing with Dr. Bain, or with any other physician from The Hospital for Sick Children, prior to delivering your reporting letters to Mr. Wiley?

A. No, I don't recall that I did.

Q. And that includes, Doctor, any pharmacologist from The Hospital for Sick Children, or any biochemist?

A. That is correct, that includes those people.

Q. Doctor, you have told us - as

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you have told us about the reports and the data that you did receive from the Centre of Forensic Sciences as part of the review that you undertook, did you leave with Mr. Cimbura at any time and review with him the data which he had compiled?

A. Yes, I did, I spent one day reviewing both some literature that he had as well as some details of some of the results, some of the studies he had done looking at his methods that he had used in his laboratory and discussing specific questions I had about the analytical procedures and calculation procedures and so forth.

Q. Was that done, Doctor, by you prior to delivering your report to Mr. Wiley?

A. Yes, it was.

Q. And Doctor, we know that you had made available to you Dr. Hastreiter's case summaries with respect to these cases. Did you before delivering your reporting letters to Mr. Wiley meet with or otherwise discuss with Dr. Hastreiter the likely cause of death, or the possible involvement of digoxin in the deaths of any of these children?

A. No, I never did discuss anything specifically with him. We were together in one meeting in the fall of 1982 in the Coroner's office

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with a number of other people, where general issues regarding several cases were discussed in the context of the police investigation, in fact that was my first exposure to the whole issue and was in fact an orientation day for me. We were both at that meeting but other than that contact I really didn't discuss anything in detail with him prior to my submitting the report.

Q. Do you recall when that meeting was, Dr. Kauffman, that you attended?

A. I would have to look it up, but I think it was in October or November of 1982.

Q. We have heard something in these proceedings, Doctor, about a meeting which took place at The Hospital for Sick Children on September 13th, 1982, at which the medical experts who were present were asked to express their views as to the possible involvement of digoxin intoxication in the deaths of these 36 children, were you present at that meeting, Doctor?

A. No, the meeting I was referring to was August 27th.

Q. And you have told us that that was by way of an orientation day or meeting for you?

A. Well, it was a scheduled meeting

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between the Crown Attorney's staff and the Coroner and a number of consultants that they had engaged and I was one of those people. It just happened that I was a newcomer at that point in time, other people had been involved earlier.

Q. Thank you, Doctor. Doctor, could we turn then if you would please to the first reporting letter that you prepared for Mr. Wiley, the one dated December 16th, 1982.

MR. SCOTT: Before we move on, I could save this for cross-examination, but I wonder if Miss Cronk can tell us if he has any minutes of that meeting, or if my friend --

THE COMMISSIONER: We may have been through this before, is this not one of the ones --

MR. SCOTT: Have we, well, I am sorry.

THE COMMISSIONER: No, no, Mr. Young is not throwing these minutes away.

MS. CRONK: To assist you, Mr. Commissioner, you will recall that on Thursday last, or Wednesday last, the production of these minutes arose and Mr. Lamek at that time indicated that it was the position of Commission Counsel that certain portions of those minutes may very well be relevant to the evidence of Dr. Hastreiter, because he is

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recorded as having expressed some views with respect to cause of death at that meeting. Mr. Young as I understand it objected on behalf of the Police to the production of a number of sets of minutes including those particular minutes.

THE COMMISSIONER: I am not sure whether we have his final answer yet, have we?

MR. YOUNG: I think you do, Mr. Commissioner.

THE COMMISSIONER: You are not agreeing to the production of those --

MR. YOUNG: We don't agree.

THE COMMISSIONER: How far have we got on the Police report generally?

MR. YOUNG: An expurgated copy was given to Mr. Lamek late last week.

MR. SCOTT: Well, Mr. Commissioner, I am sort of a newcomer here and perhaps I can be fitted into the picture. Bearing in mind that we have received I think through Mr. Lamek's good offices the minutes of what look like a high-powered Crown/Police Meeting for September 13th.

THE COMMISSIONER: Yes.

MR. SCOTT: It seems to me that at a certain point we have to stop relying on my friends'

CC.10

good will and impose an order on them.

THE COMMISSIONER: No, you have a little more, not much more, because I have read this report and I haven't yet though had to apply my mind to the problem.

3M/ak

If Mr. Young has now decided how far he is prepared to go then what I was intending to do was to summarize all the rest of the things from the police report and if necessary we will have an argument on whether it should be produced or whether it shouldn't be produced. This one is Minutes of August 27th and they are not to be produced and I take it the reason being they having nothing to do with cause of death, is that it?

MR. YOUNG: That is our position. With the greatest of respect to my friend Mr. Scott he was not here last week. We went through this exercise ---

MR. SCOTT: No respect is required for that, I wasn't here.

MR. YOUNG: Very well. In any case, Mr. Commissioner, it is our position that the bulk of the minutes that have not been introduced to date are not relevant. If Mr. Lamek approaches us or you, sir, approach us and tell us that there are portions that you believe are relevant, we will certainly consider that and we may not object. At this time, we don't feel that there are other relevant portions that should be submitted.

THE COMMISSIONER: Well, I think

Mr. Scott and others are probably entitled to know what the subject matter is of the minutes but without knowing in detail what they say before he can take a position as to whether they are relevant or not ---

MR. SCOTT: Well, may I go at it this way. It seems to me that this is a meeting at least at which this witness was present. It will serve none of us any purpose except to give us a trip to Detroit to have you declare next week that we can have it. We need it now and I would ask you, sir, if you review the minutes and tell me there is nothing relevant in it, well then, I have to be bound by that.

THE COMMISSIONER: Bearing in mind that we are not investigating the police investigation beyond May of 1982.

MR. SCOTT: I understand that.

THE COMMISSIONER: So that if this merely has to do with that and has nothing to do with the cause of death and has nothing to do with the investigation of the police before that time then it probably will not be.

MR. SCOTT: Yes, I understand that.

THE COMMISSIONER: Have you any comments you want to make on this?

MR. LAMEK: Only one very brief one, Mr. Commissioner. Nice to hear Mr. Scott back again, but that wasn't what I was about to say.

MR. SCOTT: I will be here more, it is my week.

MR. LAMEK: As I said last week, the minutes of the August 24/27 meeting, whatever it is, are minutes which in my view contain certain few extracts which are relevant to the question of cause of death. I would certainly propose to offer those extracts when Dr. Hastreiter was here and it may be there will be objection to them, it may be possible to do that while Dr. Kauffman is still here.

THE COMMISSIONER: Was there anything said by Dr. Kauffman or reported to have been said by Dr. Kauffman?

MR. LAMEK: I do not recall anything to that effect, Mr. Commissioner, but I will check them again and I will advise you and everybody else, sir.

THE COMMISSIONER: Yes, all right.

MR. SCOTT: Well, I would just like to be on record that to receive them next week will not be of any assistance when this witness has happily returned home.

by the time you attended the August 27th meeting formulated any opinion with respect either to the cause of death of these children or the possible involvement of digoxin intoxication in any of their deaths?

A. Well, at the time I attended that meeting I had no knowledge upon which to base an opinion. That was my first introduction to the entire issue. So, I don't remember what I said at that meeting but it is unlikely that I voiced any opinion on any case because I simply didn't have the knowledge to do so.

Q. Thank you, Doctor.

Doctor, could I ask you now if you would, please, to turn to page 1 of your first reporting letter to Mr. Wiley. That is the letter dated September 16th. As I read your first reporting letter, Doctor, there is no overall summary section to your report but I note that it deals in some detail with 10 cases but with no others.

At page 1 of the reporting letter in paragraph 2 you indicate that the cases of 10 patients were to be reviewed in detail in your report but in the remainder of the cases, and I am quoting:

"...there was either inadequate

"information upon which to base a detailed review or there was no objective evidence of digoxin toxicity."

The first statement I suggest is perhaps self-explanatory, Doctor, but I confess I had some difficulty with the latter part of that statement. Can you help us as to what you meant when you stated that there was no objective evidence of digoxin toxicity in those cases other than the 10 which you reported upon in this letter?

A. I was referring primarily to lack of any digoxin measurements, also lack of electrocardiographic evidence, if that was on the chart, or any other laboratory evidence which might suggest digoxin toxicity, such as an elevated potassium level or the patient being on digoxin and having compromised kidney function and things like that.

Q. Would I be correct, Doctor, in inferring from your statement, to which I have just drawn your attention, that in some cases then there was simply in your view inadequate information to allow you to form an opinion?

A. That is correct.

Q. All right.

A. In some cases.

Q. Thank you, Doctor. The next two and a half pages of your first reporting letter are devoted to what you have described by way of introduction as general comments regarding the interpretation of digoxin assays on ante mortem and post mortem sera, fresh post mortem tissue and fixed and exhumed tissues. As you will perhaps appreciate, Doctor, we have heard evidence from a number of witnesses that the variety of specimens taken from these 36 children and the manner in some instances of their sampling gives rise to a number of problems of interpretation. I take it that it was to those types of problems of interpretation that you were addressing yourself in the first pages of your reporting letter?

A. Yes, that is correct, because I felt that I had to set the tone for any judgments that I made to lay out the caveats that had to be included in those and to try to convey the uncertainty that was inherent in certain of the types of measurements that were made.

Q. Doctor, may we turn first then if you would to the issue of post mortem serum levels. I would ask you whether in your view there are

particular problems of interpretation or difficulties of interpretation that arise with specimens of that kind?

A. Yes, there are. I suspect not having been here before, but I suspect you have heard this alluded to before. It is I think well documented in the literature that following death there frequently is a change in the serum concentration of digoxin in a patient who has been receiving digoxin or who has received digoxin prior to death. This is time related following death. It seems to be variable depending on the location from which the sample is obtained and it seems, even within those variables, seems to be quite variable from individual to individual. Is that responsive to your question?

Q. Yes, thank you, Doctor.

A. The data that I had seen at the time I wrote or prepared this report indicated to me that the digoxin in serum following death could change or vary anywhere from no change at all up to threefold increase following death, in the serum or in the blood.

Q. Doctor, as you anticipated, we have indeed heard evidence with respect to the phenomena whereby the concentration of digoxin in

serum can under certain circumstances elevate post mortem after death. That has been referred to in these proceedings as the multiplier effect. Is the range that you have just referred to, that is, from zero up to 3, the range of multiplier in post mortem blood specimens which you feel reflective of the reported cases to date in the literature?

A. Well, at the time I wrote the report that's what I was using; subsequent to my report during this past year, Dr. Hastreiter's group has submitted, has published a paper in which they looked at this factor in a number of infants at their hospital and have, as I understand it, as I recall from looking at that paper several months ago, they documented a multiplier as high as fourfold, but I was not aware of that at that time, that paper had not been published at the time I prepared this report.

Q. Doctor, by referring to the minimum of the range as zero, I take it you were suggesting in some cases there is no elevation at all?

A. That is correct.

Q. All right. So that the factor does not appear, based on the reported cases to date, to be a universal one in the sense that it happens in every instance?

A. It is extremely common, but I don't think it occurs consistently in every individual.

Q. All right.

THE COMMISSIONER: Miss Cronk, have we that paper, has that been put before us?

MS. CRONK: We do have the paper, sir. In fact, I believe it has not been marked as an exhibit and I will undertake to get copies of that and see that it is marked while Dr. Kauffman is here.

THE COMMISSIONER: Yes, all right.

MS. CRONK: Q. Doctor, we have heard from other witnesses that a possible cause of the elevation of the digoxin concentration in post mortem blood as compared to ante mortem blood may well be the redistribution of digoxin from tissues into serum following death. Is that a view to which you would ascribe?

A. Yes, it is. I suspect that there is redistribution from red blood cells, from various other tissues including skeletal muscle, myocardium, skin, brain, a lot of tissues within which digoxin may be present in fairly high concentrations compared to blood; liver, lungs and so forth.

Q. Doctor, other than the redistribution if you will of digoxin from tissues

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into serum following death, is there any other explanation which you feel is reasonably and scientifically to be advanced to explain the elevation of concentrations in post mortem serum samples?

A. I really have not been able to find another explanation which makes sense to me.

Q. Thank you, Doctor. Doctor, other than the difficulties which arise because of the multiplier effect, or the elevation between ante mortem and post mortem specimens, are there any other difficulties or problems of interpretation which in your view arise with respect to post mortem serum samples?

A. I suppose one could raise a number of questions which in my mind are less well documented. One has to wonder if there is any change in the breakdown of the digoxin molecule itself which might alter the apparent concentration. One has to wonder if the assay employed measures both breakdown products as well as the digoxin itself or whether there may be other substances released following death which may interfere with the assay antibody and produce apparent elevations in digoxin. I think we have some evidence, at least in fixed tissues from

Mr. Cimbura's work, that there is some breakdown and that one can indeed distinguish between digoxinlike substances and actual digoxin. Whether or not there is any other interferring substance or simply this is a result of metabolites of digoxin being present, I really don't know.

Q. Doctor, when an attempt is made by those qualified to do so to interpret digoxin concentrations found in post mortem blood specimens, need we in your view be concerned as well with the nature of the specimen involved and the sampling technique used to obtain the specimen?

A. Well, that appears to be a very important issue. As I said, the location from which it is obtained is very important. It seems to be one of the variables which influences the apparent increase in digoxin concentration. Whether or not whole blood or serum is measured could influence that too. Another issue that has come to light during the past year is the issue of obtaining blood post mortem from whole blood from body cavity, so-called gutter blood and what variability that may introduce into the apparent concentration of digoxin.

Q. All right. Doctor, I will return to the issue of gutter blood specimens in due

course but for the moment, in your opinion as a pharmacologist in attempting to interpret these post mortem digoxin levels in post mortem blood specimens, do you consider a whole blood specimen or a serum specimen to be one preferable to the other?

A. I don't think one is particularly preferable to the other but I don't think you can necessarily equate them because, particularly in infants and small children, it appears that more digoxin is bound to red blood cells during life than is in solution in serum. So, if one samples and measures digoxin in whole blood than you would in serum, in post mortem blood samples it sometimes is difficult to separate the red cells from the serum and get a pure serum sample because the red cells tend to break up following death and release some of the material inside them. So that sometimes, many times post mortem it is difficult to get a pure serum sample with which to measure digoxin.

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Q And the sample of preference do I correctly take it then, Doctor, were it possible reliably to do so you would prefer that the specimen be a serum specimen?

A. Yes simply because that is the - we have come over the past 10 years to interpret digoxin concentrations in term of serum concentrations and so to relate a given concentration to past experience it would be easier to do it currently with serum concentration versus the whole blood concentration. And in that sense I would prefer that.

Q. And that I take it, Doctor, flows from the fact that reported cases deal traditionally with digoxin concentration measured in serum and they afford a benchmark against which to measure post mortem serum levels?

A. That is correct.

Q. Doctor, you have told us as well your view as to the likely range of multiplier which may take effect between an ante mortem and a post mortem blood specimen.

Dr. Speilberg of the Hospital for Sick Children has as well testified before the Commissioner.

Do you know Dr. Speilberg?

A. I know him, yes.

Q. He has testified, and this evidence, Mr. Commissioner, is now found at Volume 54, page 2045 - loss of binding or redistribution of digoxin can as well occur in living patients.

He said in this regard, and I am quoting:

> "...without any exogenous administration of digoxin, the possibility exists, under certain pathophysiologic conditions - the published condition being renal failure - for reasons that we don't fully understand, digoxin levels can rise in the absence of administration of digoxin,"

And he suggested, Doctor, and I tell you that there may be a number of causes for that phenomenon. The first that he suggests is loss of digoxin from tissue because the binding sites may have become damaged or the tissues may have died or other things may be displacing the digoxin.

He suggested as well that renal failure may account for the phenomena or the other factors, interplay of other drugs such as quinidine may cause that to happen. Or that indeed tissue death or

necrosis of various tissues may cause that to happen in life.

My question to you, Dr. Kauffman, is that a phenomena with which you as a pharmacologist are familiar?

A. Yes, it is.

Q. In your opinion, Doctor, is there any particular explanation or explanations which from a pharmacological point of view appear to afford the best explanation for that phenomena?

A. I don't think I can give you a simple yes answer to that.

It has been demonstrated that the drug-drug interaction such as seen with quinidine does elevate the digoxin serum concentration in patients.

The mechanism by which that occurs I don't think is fully understood. There have been studies published looking at changes in tissue - attempts to look at changes in tissue concentrations, attempts to look at changes in clearance of the drug. In other words rate at which it is excreted from the body.

I don't think it is clear yet what the mechanism is but it is a well documented phenomena. that is the quininine and the drug-drug interaction.

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I don't think it is clear yet what the mechanism is but it is a well documented phenomena. that is the quininine and the drug-drug interaction.

In terms of the tissue damage, tissue deaths, acidosis, hypoxia, those kinds of phenomena in the living individual, yes, I would agree there I think there is a potential for redistribution of digoxin.

The renal failure thing is a little bit muddy in my mind. It is true that as far as I know it is true that digoxin, apparent serum concentrations of digoxin may increase in a patient with compromised kidney function.

There is one paper, an adult that I am aware where this was documented, without any further administration of digoxin over a period of several days.

It has also been documented that individuals with renal failure may have circulating some substance that interferes with the antibody that is used in the digoxin assay, so that I am not sure in my own mind whether this apparent increase in serum concentration in some patients may be just an apparent increase due to an interfering substance which makes the level look higher than it actually is or if it is a true redistribution of digoxin in the serum with a true increase in the serum concentration in patients with renal failure.

Q. Doctor, you have explained your views as to the interpretive problems that arise with post mortem blood specimens.

Do all of the factors which you have outlined in terms of difficulty of interpretation apply equally to the interpretation of digoxin levels in ante mortem blood specimens?

A. In terms of serum concentrations?

Q. Yes.

A. No, I don't think they apply equally. I think that ---

Q. I am sorry, with the obvious exception of the multiplier effect.

A. Yes. I am not sure I understand the point of your question.

Q. I am sorry, Doctor. To put the question more clearly are there problems of interpretation which you consider to particularly arise when one is trying to interpret a digoxin level in an ante mortem serum specimen as distinct from a post mortem serum specimen?

A. One needs to be sure - there are problems that are unique with multiple dosing of digoxin.

For example, one needs to be able to

be able to interpret the concentration, one needs to be certain you have obtained the blood sample long enough after the previous dose that full absorption and distribution has taken place so that you don't misinterpret the concentration. And that the guidelines for that clinically are generally at least after six hours. For practical purposes we usually recommend in our Hospital they be obtained at 12 hours just before the next dose.

If you obtain a specimen too soon after a dose you will very likely measure non-steady state concentrations which will be higher than the steady state concentrations which will give you misleading interpretation.

One has to consider the assay that is being used and for standard procedure now, one of the radioimmunoassay kits or the fluorescent polarization procedure and in some hospitals the colorimetric procedure immunoassay is used. These are all antibody based studies and assays and are subject to substances that may interfere with the assay and as we have learned during the past year, particularly premature infants and infants up to three months of age, people with renal failure,

people who have too much salt and water on board, various situations, both age and pathologic situations can result in interfering substances which may give erroneous digoxin assays with that particular technique, so there are problems in interpretation ante mortem that one must be aware of.

Q. You have referred us in that regard, Doctor, to both the issue of the timing at which the sample is taken and as well to the methodology employed for the assay technique itself.

When we come, Doctor, to the issue of digoxin concentrations found in fresh or frozen tissues are there problems you consider particular to interpretation of those kinds of concentrations in those kinds of specimens?

A. I view the fresh and frozen tissue as probably reflecting as close as we can get to the concentration that existed in the tissue at the time of death, and those measurements are subject to whatever the problems might be for fresh tissues obtained at any time.

The problem with tissue concentrations, even fresh tissue concentrations, is that there is a tremendous overlap between concentrations associated

with apparent toxicity and concentrations seen in patients who are taking digoxin who don't have any apparent toxicity. There is tremendous overlap. There is tremendous variation. More than tenfold variation from individual to individual. In either a therapeutic or associated with apparent toxicity. So that makes it difficult in an isolated situation to say that the single measure is toxic or non-toxic unless it is obviously different, higher than any reported concentration associated with therapeutic dosing or with toxic doses.

Q. Doctor, if I could stop you there just to make sure I understand what you said. You have told us there is a tremendous area of overlap between concentrations in various tissues as between therapeutic ranges and as between toxic ranges.

How then with certainty if it is indeed possible at all can a pharmacologist judge whether a particular concentration in fresh or frozen tissue does fall within the toxic range?

A. I don't think you can interpret digoxin concentrations in isolation. You have to look at them in the context of the entire clinical picture.

For example, if you measure concentration X and it could be within a range that has been reported

as toxic or a range seen in patients with toxicity and this patient has no clinical evidence of toxicity, I would not call that a toxic level in that particular patient.

On the other hand if the patient had other signs of toxicity such as symptoms or electrocardiographic evidence, then I would accept that that could be a toxic concentration in that patient. So you have to interpret the drug concentration in the context of the entire picture. I don't think you can interpret it in isolation.

Q. I take it then, Doctor, there are two features of particular assistance in that situation. The first being the actual clinical condition of the child and whether or not the patient had been exhibiting any signs which clinically could be interpreted as symptomatic toxicity?

A. That is right.

Q. And secondly, Doctor, it is of obvious relevance from what you have said to compare the concentration measured with those that have been reported in other cases in the literature to determine whether it falls within what has been reported as a therapeutic level or a level beyond that which was considered in the published literature as being

therapeutic?

A. That is right. Either it has to be so different from previous experience that it is clearly toxic or it has to be associated with other supporting clinical signs and symptoms and objective evidence that the patient was experiencing toxicity.

Q. Doctor, you have told us that the literature review which you undertook when you accepted the assignment of reviewing these charts, did you as part of that review seek to observe what had been reported in the literature in fresh and frozen tissue specimens as the ranges of concentrations to be taken as within the toxic category in samples of that kind?

A. Yes, I attempted to find whatever literature I could to get some idea of what ranges had been recorded and that one could use as a guideline for making judgments.

Q. Right. Amongst Mr. Cimbura's findings, Dr. Kauffman, you may recall in his first report dated January 11th, 1982 - perhaps you have a copy before you?

A. I think I have a copy of that here some place.

Q. If you could turn to page 4 of

his report, Doctor. Do you have that, Doctor?

A. Yes.

Q. Item No. 3 on page 4, Doctor, Mr. Cimbura records that the range of digoxin values found based both on literature reports and research conducted at the Centre for Forensic Sciences found in patients on digoxin therapy in ventricular muscle of infants was between 49 and 975 nanograms.

He suggests further in Item 3 that the range of concentrations reported in specimens of that kind in cases of fatal poisoning was between 108 to 1240 nanograms per gram.

Based on your review of the literature and your knowledge of the area, Doctor, is that range of toxic values in heart muscle specimens one which you agree or disagree?

A. Yes, I would agree with that.

Q. And, Doctor, if you examine paragraph 4 on page 4 we find that Mr. Cimbura sets out similar ranges again based both on literature reports and his own research with respect to values found in lung specimens and suggests that the concentrations reported in those kind of specimens in cases of fatal poisoning was between 4.2 and 100 nanograms per gram.

Once again I would ask you, Dr. Kauffman, based on your own research and knowledge of the area is that a range in fatal poisoning cases that you would accept as being reliable?

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A. Yes, in general I would agree with that. I wouldn't get hung up too hard on the exact numbers, but that kind of range is what I would agree with.

I some time ago looked at some of this material and tried to look at it for specifically some of the data that Dr. Hastreiter had published where he had given averages within different tissues and then 1, 2, 3 standard deviations away from the average and I don't know if this 100 is within two standard deviations from his averages or not but it is in this kind of range.

Q. And I take it, Doctor, that your caution with respect to the numbers themselves arises by virtue of the area of overlap that you have described in trying to postulate these kinds of ---

A. Yes, that is correct.

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Q. Doctor, I would ask you if you would to turn to page 7 of the same report at Note 2, Dr. Kauffman, on page 7, Mr. Cimbura indicates that concentrations of digoxin in the liver of persons on digoxin therapy are reported to range between 2.1 and 190 nanograms per gram; while in digoxin fatality cases the concentrations of the drug in the liver are reported to range between 35.3 and 580 nanograms per gram. Once again as a general statement of the applicable ranges for digoxin fatality cases, is that a range that is acceptable to you?

A. Yes, those are the kind of ranges that I recall reviewing in the literature.

Q. Doctor, other than the area of overlap which you have described between therapeutic values and toxic values in fresh and frozen specimens, you have indicated in your reporting letter to Mr. Wiley that a further problem arises, and that is what you have described as the distribution characteristics of digoxin per se. Can you help me, Doctor, as to what problem you had in mind when you listed that as a factor of concern in interpreting this data?

A. Well, there are several issues here, one is that for a given serum concentration, the concentration in tissues tends to be higher if the

FF.2

patient has been on chronic therapy as opposed to following a single dose.

Secondly, there I ran across some minimal evidence suggesting that in large overdoses the distribution of digoxin between tissues and serum may not be quite the same as it is - this was in several adult poisonings, may not be quite the same as it is when the patients are on therapeutic doses.

Thirdly, there is evidence that infants and small children tend to have more digoxin in tissues and red blood cells for a given concentration in the serum than do adult patients, which makes it somewhat tenuous to directly extrapolate adult tissue concentrations to infants. So those are the three areas that concerned me at that time and still do.

Q. I take it that the latter difficulty, Doctor, would be equally applicable whether one was considering any concentration found in fresh tissue, or indeed a concentration found in fixed or exhumed tissue, there would still have to be caution applied as to the difficulties of comparing values found in adult specimens as opposed to tissues which may apply, levels which may apply in tissues of infants?

A. I suppose so. I think there are

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other problems with fixed and exhumed tissues that probably overshadow this particular problem, that make it relatively minor in that situation.

Q. Well, Doctor, dealing first with fixed tissues, could you outline for us if you would the particular problems of interpretation which you feel arises in the case of digoxin values found in those kinds of tissues?

A. There are several problems that I am aware of.

THE COMMISSIONER: Before you go on, Doctor, I take it we find most of this, what you are giving is found in your report, is it?

THE WITNESS: Yes, it is essentially as I have stated in my report.

THE COMMISSIONER: I wonder if you or Miss Cronk would point out the paragraph.

MS. CRONK: I am sorry, sir. The matters just raised by Dr. Kauffman with respect to fresh and frozen tissues, Mr. Commissioner, are set out in general form on page 2 of the first reporting letter in the middle full paragraph on that page.

THE COMMISSIONER: The first full paragraph, yes, all right.

MS. CRONK: Q. Is that correct, Dr. Kauffman?

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A. Yes, that is correct.

Q. And your comments, Doctor, and correct me if I am wrong, with respect to the problems of interpreting post mortem serum levels are set out in the first paragraph on page 2?

A. That is correct.

Q. And where in this report, Doctor, do we find your specific comments with respect to the interpretation problems that arise when we are concerned with fixed or preserved tissues?

A. I think that is dealt with in the third paragraph on page 2, it starts on page 2. A variety of additional problems are encountered in the interpretation of digoxin assays on preserved autopsy tissues.

Q. And to complete the matter, am I correct in inferring that your comments with respect to the difficulties which arise with exhumed and embalmed tissues commence at the top of page 3 in the first two paragraphs?

A. That is correct.

THE COMMISSIONER: Yes, Mr. Olah?

MR. OLAH: I wonder if Miss Cronk can help us, or whether the doctor could indicate whether the tissue ranges he talked about and agreed with

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Mr. Cimbura are adult or infant ranges?

THE COMMISSIONER: The tissue ranges?

MR. OLAH: Yes, sir, you will recall the doctor agreed with the series of ranges that were outlined in Mr. Cimbura's report and I was not aware whether those related to adult ranges or infant ranges?

THE WITNESS: I think they include both. If I remember right, Mr. Cimbura specified infants specifically when he was dealing with the heart tissues. I can't find the page now where that information is.

MS. CRONK: Q. To be of further assistance, sir, it is my recollection, as it is of Mr. Lamek, that Mr. Cimbura when giving his evidence indicated that the ranges quoted, to which I directed Dr. Kauffman, were taken from both the literature published on adult and infant values in therapeutic cases and toxic cases too.

A. That was my recollection too. On page 4 of his report that we were just looking at, on page 4, paragraph No. 3, he does specify ventricular muscle of infants. But I did look at literature on both adults and infants published, as well as some unpublished literature that Dr. Hastreiter had made available to the Crown Attorney prior to my involvement.

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Q. Doctor, based on your review of the literature which pertained particularly to the range of levels which might be found in infants both after therapeutic administration and in cases of digoxin fatality. Are the ranges quoted by Mr. Cimbura to which I have referred you in line with the ranges which you understand to be applicable for infants?

A. Yes, I think so.

Q. Thank you, Doctor. Doctor, we were about to turn then if you would please to an elaboration of the difficulties of interpretation which you feel apply particularly to fixed or preserved autopsy tissues. Could you outline for us please, Dr. Kauffman, what your concerns are in that area?

A. Well, one major concern is that when the tissue is placed in the fixative, the digoxin is soluble in the fixative and tends to be dissolved out of the tissue, or leached out of the tissue and moves into the solvent, or the fixative solution. So that over time the amount of digoxin in the fixative decreases and the concentration in the fixative solution increases until an equilibrium develops of some sort depending on the relative solubility in the tissue, the particular tissue, and the solubility of digoxin in the fixative.

FF.7

Another thing that seems to happen is that to some degree the digoxin can break down in the fixative, so that the amount of major digoxin may decrease for that reason. So it becomes very difficult taking a piece of tissue out of fixative after some period of time to know what that measurement means other than digoxin is present, it is virtually impossible to quantitate.

Mr. Cimbura attempted to do this in some cases where only one tissue was in the fixative. If you have combined two different organs, two or more different organs in the same jar then it essentially is impossible. When one tissue was in the jar he attempted to do this by knowing the weight of the organ, and the heart, if it was the heart, knowing the concentration at the time he measured it in that tissue, the concentration in the fixative fluid and the volume of the fixative fluid and by back extrapolation could estimate a concentration which may have existed in the tissue prior to being placed in the fixative. There are some problems with doing that, but that was the best estimate, under ideal conditions in fixative that is the best you can do under ideal circumstances with fixed tissues. I think it is-a quantitative interpretation of digoxin

FF.8

results from fixed tissues is fraught with problems, and I think it is helpful essentially only to say that the digoxin is there, or is not there.

Q. Then finally, Doctor, could you outline for us the problems which you feel to apply when dealing with exhumed or embalmed tissues for the purposes of interpreting digoxin concentrations?

A. I think this is an area where we have the least knowledge about what happens and can think of a number of problems, and have very little evidence one way or the other as to how significant these problems are.

Digoxin is unstable in certain embalming fluids and can undergo chemical degradation following embalming. So if that happened you would project that the concentration of digoxin in the embalmed body would decline over a period of time.

We know essentially nothing about redistribution of digoxin in tissues following death over a long period of time, but we suspect that binding changes, not because of, but after the tissues die. I would predict that when more of the drug becomes unbound it tends to re-equilibriate within the different tissues so that the concentrations in the high concentration tissues would decrease with time,

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and the concentration in low concentration tissues - or the concentrations were low prior to death would tend to increase, so that could be very confusing.

Q. Can I stop you there for just a moment, Doctor?

A. Yes.

Q. Is that a problem unique to embalmed or exhumed tissues? I would have thought that would apply equally to any tissue specimens with which you were concerned?

A. It is only unique in that the embalmed body is intact. If you have isolated organs from an autopsy, there is no place else for the material to go unless it is in the fixative solutions and it leaches into the solution.

In the intact body then you can, I would predict that you would see digoxin diffusing from one tissue into another over a period of time, particularly adjacent tissues, so that the concentrations could change.

Q. And are you talking there, Doctor, about a matter of relative concentration such that the higher the concentration in tissue (a) the greater the likelihood that some of that would seep or displace into adjacent tissue with a lower initial concentration?

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A. Yes, you would predict that it would move from higher concentration to tissues or body fluids of lower concentration.

Q. I am sorry, Doctor, I interrupted you.

A. That is all right. Another problem is - it is probably the case depending on the burial conditions and the length of time that the amount of water in the body declines with time so that the body becomes, the tissues become drier and drier, this is referred to as desiccation of the tissues. When my secretary first typed this she typed "desecration". When that happens, and you express the amount of digoxin in terms of tissue weight, as you lose water you lose tissue weight. So if you have fresh tissue and you express the digoxin concentration in terms of micrograms per gram of wet tissue, and then you desiccate or dry that tissue and you lose the weight from losing the water and you express that same amount of digoxin in terms of a gram of tissue, it will appear to be higher because the tissue weighs less, the same piece of tissue will weigh less. So it is conceivable that in an exhumed tissue which has undergone drying, other things being equal, the apparent concentration could appear higher than it originally was simply because the weight of the tissue is less due to loss of water.

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So, you can see that these various factors can work in opposite directions. Some of them could tend to decrease the apparent concentration, others might, particularly the last one, the desiccation, might appear to increase or would increase the apparent concentration. I have no idea at all to what degree these various factors play a role and to what extent they change the digoxin concentration of various tissues in exhumed and embalmed bodies and it is this uncertainty I think that handicaps us in using these concentrations in any quantitative sense.

Q. Well, Doctor, apart from being able to rely on the concentrations found in exhumed tissues in any quantitative sense, do they, having regard to the difficulties you have outlined, serve any useful purpose at all in your view in terms of interpreting the presence or absence of digoxin and the quantity of digoxin in the specimen involved?

A. They can tell us that digoxin is there, and that can be helpful. That alone I don't think can tell us that the patient died of digoxin toxicity. That, in conjunction with other corroborative evidence could support the theory that the patient died of digoxin intoxication.

Q. Well, Doctor, [illegible] to approach

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that from another point of view for a moment. Quite apart from the issue as to whether or not digoxin caused the death of any particular patient, can you, on the basis of concentrations reported in exhumed tissues alone make any reasonable scientific conclusions with respect to digoxin toxicity, or is the extrapolation that is possible confined to confirming or negating the presence of digoxin in the patient involved?

A. I think essentially it is confined to confirming or negating the presence of digoxin. I think it is very difficult to use digoxin concentrations in embalming and exhumed tissues by themselves to make a definite judgment one way or the other that digoxin was responsible for death. It is just too difficult to interpret them, there are too many uncertainties and unknowns.

Q. Doctor, given all the various difficulties that you have described with tissue specimens at large, do you place any higher degree of confidence on concentrations reported first in fresh or frozen tissue specimens than in fixed or exhumed specimens?

A. Yes, I place a much higher confidence on fresh or frozen specimens, obviously,

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than I do on fixed or exhumed tissues. I think that fresh autopsy material can give you some idea of what was there at the time of death. I think, as I have said, that there are so many problems with the fixed tissues and the embalmed and exhumed tissues that it is very difficult to know what the concentration actually means.

Q. Do you place then, Doctor, the same, perhaps I can describe it as low level of confidence in concentrations reported in fixed specimens as you do in exhumed specimens or do you draw a distinction between those two in your mind?

A. Well, I would differentiate them only to the extent that I think we know a little bit more about what the nature and degree of the changes are with fixed tissue because there is a little bit of - that is a little bit of information from study that can tell us how, to what degree the changes can be, to what degree their concentrations change. But I don't really think that gives us any more competence in interpreting in an individual patient, the concentrations that's measured, I think they are both very problematic.

Q. Doctor, does the fact that a fresh tissue specimen may have been frozen prior to

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assay affect the level of confidence which you would attach to the concentration reported?

A. If it was frozen immediately when it was obtained, within a reasonable time, I think I would probably treat that essentially as a fresh specimen.

Q. All right.

A. In fact, we use freezing frequently to preserve specimens for later assay, that's a fairly standard procedure.

Q. Doctor, you have told us earlier that, as you understood it, when you were asked to undertake the review of these cases you were being asked, and I believe your language was to assess the likelihood of the possible involvement of digoxin in the deaths of any of these children, do I express that fairly?

A. I think so, if I understood you.

THE COMMISSIONER: No, I think there is an extra possibility in there, the likelihood of the possibility. I think we could have left out one or the other.

MS. CRONK: I'm sorry, the likelihood of the possible involvement of digoxin - well, I will

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take out the possible.

THE COMMISSIONER: Likelihood of the involvement is enough, but perhaps I'm wrong.

MS. CRONK: Q. Was that, in your mind, the primary objective of undertaking the review, Doctor?

A. Yes, I think what I was asked to do was to review the cases and, looking at the entire picture with the information I had at hand, to try and make a judgment as to what the likelihood was that the infant's death was related to digoxin.

Q. All right. Did you as well, Doctor, in considering each of these cases, address your mind to whether any other medication or drug may have played a part in the death of the child?

A. Yes, I did, that was a part of the entire picture. So, I looked at other drugs that I was aware were being given or had been given and could or could not have played a role in the infant's death.

Q. Did you as well, Doctor, in approaching your review of these cases, address your mind in each case to the disease state of the child and the child's clinical condition with a view to determining whether that could account for the

terminal events suffered by the child and the actual cardiac arrest suffered by the child?

A. Yes, I did. As I have said before, you cannot interpret the digoxin data in isolation, you have to interpret it in the entire clinical, in the context of the entire clinical picture for each case. So, I looked at all the clinical data available to me, the laboratory data, not the digoxin data but the clinical laboratory data when it was available, the autopsy results, and then the other drugs that had been prescribed, the clinical course of the patient, the description of the terminal event and then try to relate that to whatever digoxin data was available on that particular patient.

Q. Doctor, as I understand it on a review of your two reporting letters, in some instances as well you attempted to estimate the minimum dose of digoxin which might have been administered to the child and where possible the maximum amount of dose that might have been administered as well. Do I have that correctly?

A. I tried to do that in several cases, yes.

Q. All right. Doctor, was it also

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part of your review to consider whether or not the particular clinical condition or disease state of the involved child rendered the child more susceptible or more vulnerable to digoxin toxicity than a child in a different condition?

A. Yes, I made that a part of my evaluation.

MS. CRONK: Mr. Commissioner, I am about to turn to the specific cases, could we take our break now?

THE COMMISSIONER: Could we talk 15 minutes then.

---Short recess.

---Upon resuming.

THE COMMISSIONER: Yes, Miss Cronk.

MS. CRONK: Q. Dr. Kauffman, you have told us that you reported in detail in your reporting letters to Mr. Wiley concerning 10 of the children with which this Commission is concerned. Amongst them, as I understand it, were Justin Cook, Stephanie Lombardo, Jordan Hines and Jesse Belanger. As I understand it, you reviewed the medical charts personally of each of those children. Do I have that correctly, Doctor?

A. That's right.

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Q. I take it you are aware, Doctor, that in the case of Justin Cook, digoxin was found in fresh and fixed tissues from that child's body and in the case of Stephanie Lombardo and Jesse Belanger it was found in exhumed tissues and in the case of Jordan Hines it was found in both fixed and exhumed tissues. Were you aware of the toxicology data in that regard, Doctor?

A. Yes, I am.

Q. And I take it, Doctor, that you are also aware that none of those children were known to have been prescribed digoxin during their lives while at the Hospital for Sick Children?

A. Yes, I was aware of that.

Q. Right. May we turn then, Doctor, to page 12 of your first reporting letter, if you would, for a moment, to the section entitled "Miscellaneous Comments". As I understand it, you indicate in this section of the report that the finding of digoxin in the fixed or exhumed tissues of these children - I am reading now from the second sentence of that paragraph, Doctor - indicates that these infants did receive digoxin some time prior to their death either by accident or by intentional act.

Am I correct, Doctor, that you

further concluded in respect of each of those cases that there was a high probability that digoxin directly contributed to their deaths?

A. Yes, that was my judgment at that point.

Q. And in respect of each of these four cases, Doctor, did you feel that there was sufficient data available to you to permit you to attempt an estimation of the amount of the digoxin dose that may have been administered to the child, the likely route of its administration and the approximate time of its administration?

A. Well, adequate data for that were really only available in the case of Justin Cook. So, it was difficult for me to attempt to do that with the other patients because of the lack of more specific digoxin assay results.

Q. All right. Doctor, if we can then for a moment address the final sentence in this section of the report. You indicate:

"It seems unusual that the same medication..."

I'm sorry, if we could back up to the second last sentence:

"Amongst these four infants only in

"the case of Cook was there adequate detailed digoxin information with which to make an estimate of the amount of the dose, the route of the administration of the dose and the approximate time of the administration."

Which is what you have just told us. And you then conclude:

"It seems unusual that the same medication error would occur with this frequency on the same ward during the same shift, therefore, I think there is a reasonable probability digoxin was deliberately administered to these infants."

Doctor, I will return subsequently to the basis upon which you formulated that opinion but for the present I take it that it is your view that in each of these four cases you do not consider it probable that digoxin was administered of delivered to these children accidentally?

A. I consider that possibility but I discarded it at that time as being the most likely possibility for various reasons. I don't know if you want to get into that now or not, we can if wish.

Q. I think we will come back in a moment, Doctor, to the basis for the conclusion.

A. Okay.

Q. But I take it we can agree at this stage that accidental administration, while a possibility, was not in your view a probability in these four cases?

A. That is correct.

Q. All right. Can we turn now then, Doctor, to the four specific cases. I understand that it has been some time since you delivered these reporting letters to Mr. Wiley and that you have not had an opportunity to review in detail for a second time the charts of these children, is that correct?

A. That is correct.

Q. All right. If there is anything, Doctor, in the course of our discussion to which you would specifically like to refer in any of the medical charts, please don't hesitate to ask for them.

A. Okay.

Q. Dealing first with Justin Cook, Doctor.

THE COMMISSIONER: I wonder, Miss Cronk,

if it might be wise to have the charts out.

MS. CRONK: All right, sir. The medical record for Justin Cook is Exhibit 116, Stephanie Lombardo, Mr. Registrar, that is Exhibit 78, for Jesse Belanger it is 79 and for Jordan Hines it is Exhibit 103.

THE COMMISSIONER: Yes, all right, Miss Cronk.

MS. CRONK: Thank you, sir.

Q. Doctor, you have already told us that in the case of Justin Cook it was your conclusion that there was a high probability that digoxin contributed directly to his death. Your summary and evaluation with respect to this case commences at page 3 of your first reporting letter and continues over to page 4. I direct your attention, Doctor, to the top of page 4 for the moment if you would, please. I suggest that the language of your summary conclusions with respect to this child is somewhat stronger than high probability. You indicate:

"There is no doubt that this infant received a large dose of digoxin some time prior to his death and that this was a major contributor, if not

"the sole cause of his sudden demise."

Do you see that passage, Doctor?

A. Yes, I see that.

Q. Does that passage accurately reflect the conclusion which you reached with respect to Justin Cook?

A. I think it does. I must say that at the time I dictated this I wasn't picking and choosing every word with the idea in mind of defending it a year later but I think it fairly represents my judgment at that point in time and still substantially does. I did hedge because you can't be, I couldn't be absolutely certain that because of his serious heart disease that it was the only cause. He obviously had heart disease which could contribute to sudden death at some point in time but I thought that it was certainly a major contributory.

Q. All right. Doctor, you have anticipated me because I'm about now to ask you to outline if you would please the basis upon which you formed this opinion.

A. Justin Cook, as you recall, was three months old and had been in the Hospital approximately a little less than 48 hours with severe cyanotic heart disease.

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He never received digoxin by medical order at any time during his life. He did receive a number of medications during that short hospitalization both intraveneously and orally.

He appeared to be - the evening of I believe it was the 21st of March he appeared to be relatively stable following a dose of propanolol at 1800 hours delivered to him because he had a severe cyanotic spell. And if you look at the chart as I recall he is described as becoming more pink and improving significantly at that time.

He fed several times during the evening and had stable vital signs and received another oral dose of I believe of propanolol around midnight and was described as resting quietly.

Then at 3:30 a.m. he became irritable, increasingly cyanotic, had a convulsion. His heart rate went down and then he progressed into ventricular fibrillation, approximately 30 to 45 minutes later and could not be successfully resuscitated.

A sample as you are aware was obtained during resuscitation and several assays as I recall were done on that, but the concentration measured in that sample was around 70 nanograms per mil.

In my report I think I used a number 72

but there were several numbers around that value. I don't think that is critical.

Apparently a serum sample that had been obtained the day previously was located and a digoxin assay was run on it, and the concentration was, as I recall, zero if I am not mistaken. So one thing that was very important to me was that he had had a documented serum concentration from the sample obtained the day previously which did not detect any digoxin. He had not been prescribed any digoxin and still a high concentration of digoxin was found in a blood sample obtained during his resuscitation.

In addition to that a fresh frozen specimen of the ventricular myocardium was obtained and assayed for digoxin and was found to contain approximately 1100 nanograms per gram of tissue. And then post mortem tissues obtained which were in preservatives were assayed later on and found to contain digoxin.

I did not attempt to quantitatively interpret this for reasons I have described.

He also was found to have digoxin in his small bowel at the second autopsy.

So the things that led me to believe

that he had received a high dosage of digoxin some time relatively shortly prior to his death was the high serum concentration, the high concentration in fresh frozen myocardium, the fact that he had not received digoxin at least by prescription prior to his death, and the nature of the illness being rather sudden and somewhat unexpected and not inconsistent with digoxin-induced death.

I might say that his heart disease was of the type that could have contributed to sudden death, and also was the type of heart disease that digoxin by increasing the contraction of the heart could have made his cyanosis that much worse and contributed to that mechanism.

Those are primarily the rationale for my judgment in this particular case.

Q. Thank you, Doctor.

Doctor, dealing with the severity of his heart condition and the nature of his disease state, if I can describe it that way, in your opinion could the terminal events which were sustained by Justin Cook including, you will recall, experiencing of bradycardia followed by ventricular fibrillation throughout the course of resuscitation, have been caused by his clinical condition?

A. They could have been. Could have been.

Q. And I take it, Doctor, that were that the sole or primary cause of those terminal symptoms we would still be in the position of having to deal with both the ante mortem and the post mortem serum digoxin levels that were recorded on the child?

A. That is correct.

Q. And from what you have told us, Doctor, I take it that this is one of the cases specifically where you considered that the condition of his heart disease or the severity of his heart disease could well have contributed to increasingly severe reaction in the event the digoxin was administered? Do I have that correctly?

A. I think it would have.

He was more at risk from the ill effects from digoxin than an infant with an anatomically otherwise normal heart, yes, for the reasons I stated.

Q. Doctor, it has been suggested in evidence by Dr. Robert Freedom with respect to Justin Cook that digoxin in fact in his view was contraindicated for this child.

Based on your review of his medical record and understanding his clinical condition, is

that a view with which you would agree or disagree?

A. I would concur with that.

Q. Right. And, Doctor, as well was this a case where you specifically addressed the possible involvement of other drugs or other medications in the terminal events and the cardiac arrest suffered by this child?

A. I considered those, yes.

Q. Doctor, from the medical record of Justin Cook and I would refer you to page 29 of the medical record. It is just beside you on the left there, Doctor.

A. What page, please?

Q. Page 29. We know, Doctor, from the progress notes on this child that at approximately 3:45 a.m. according to nurse Susan Nelles' note which appears on page 29 the child began to experience difficulties.

If we turn over to the next page, page 30, in combination with the nursing note we see that between 3:45 and 3:55 in the morning on March 22nd, he received or was reported to have received two doses of Inderal in the respective amounts of .4 millilitres and .2 millilitres for an aggregate of .6 millilitres.

Do you see that, Doctor?

A. I see that, yes.

Q. You indicated, Doctor, in your report to Mr. Wiley, and I would refer you to the bottom of page 3 of your first reporting letter and the top of page 4, that the Inderal so administered could have contributed to his bradycardia and arrhythmia.

Do I have that correctly, Doctor?

A. That is correct.

Q. We also note from the medical record of this child, Doctor, and you referred to some of them, that a number of additional doses of Inderal were recorded as having been administered to the child prior to his death.

There was, as you referred to a moment ago, a dose at 6:00 p.m. on March 21st, which according to the progress notes was in the amount of 3 milligrams given orally by a nurse.

There was as well, according to page 25 of the progress notes, Doctor, another dose administered at approximately 6:20. I would ask you to refer to that page if you would, page 25.

A. I have that page.

Q. And that dose, Doctor, I take it

we can agree appears from that note to have been in the amount of .078 milligrams per kilogram administered by IV.

A. I don't see the IV.

Q. I am sorry, Doctor, you are quite right. The amount of dose is set out on that page and it is in the nursing note describing those events that it is suggested that the amount was administered by IV by Dr. ---

A. The note is on page 29.

Q. No, I am sorry, Doctor, on page 27. Dose administered IV by Dr. Kantak.

I take it that is that dose - it is in respect of that dose at 6:00 p.m. in the evening, Doctor, that you suggested that he had responded?

A. Yes.

Q. The note indicates that he almost immediately pinked up?

A. Yes.

Q. And we know as well, Doctor, and you referred to this a moment ago that at 12 midnight he is recorded as having received another dose, and I would ask you in this regard to turn to page 17 if you would. This is the medication and the treatment record for the child, Doctor.

A. Yes, I have it.

Q. And at midnight on the 21st of March it is recorded that he received another dose of Inderal. This time .4 milligrams administered orally.

Do you see that, Doctor?

A. Yes.

Q. Doctor, when you expressed the opinion as you did in your first reporting letter to Mr. Wiley that the Inderal administered prior to Justin Cook's death could have contributed to his bradycardia and arrhythmias, were you taking into account all of the prescribed and recorded Inderal doses that appear to have been given to the child or were you directing your mind specifically to those two which are recorded to have been given between 3:45 and 3:55 in the morning of March 22nd?

A. I was taking into account all of the doses, but I was primarily concerned with the intravenous - the intravenous doses given shortly before his Code. The .6 millilitres given intravenously, that was my major concern when I said that it may have contributed to bradycardia.

It is known that Inderal, because of its beta blocking activity is a heart muscle depressant,

and any time you are treating a baby like this you are trying to relax the muscle just enough to open up the outflow tract to the pulmonary artery and still not suppress him so much that thereby you are going to slow the heart rate and reduce the cardiac output so it is a fine line that one walks.

I suspect that when the heart rate did slow after that, after those two IV doses of Inderal, that is why the atropine was given to try to increase the heart rate again to counteract some of the bradycardia that had occurred.

Q. Doctor, you have referred to what I think you have described as the beta blocking activity of Inderal?

A. Yes.

Q. Did I hear you correctly?

A. Yes.

Q. Could you help me as to what you meant by that.

A. Okay. Part of the innervation to the heart is from the adrenergic nervous system and the receptors which respond to stimulation from that part of the nervous system are called beta receptors, and the mechanism of action or at least one of the mechanisms of action of propanolol is to block

those receptors so that norepinephrine and epinephrine do not stimulate the heart or the nervous system, the sympathetic nervous system doesn't stimulate the heart so much so that it tends to relax the heart muscle; it tends to slow the heart rate and excess will do that to a greater degree than you wish.

Q. Doctor, having regard to the number of doses that are reported as having been given to Justin Cook in the 24 hours prior to his death, and assuming that the recorded amounts of Inderal were in fact administered to the child, would they in combination be sufficient in your opinion to have accounted for the terminal events which he suffered, the mode of death which ensued and his actual cardiac arrest and failure to be resuscitated?

A. I don't think so. These were accepted therapeutic doses, and I did not view them and do not view them as being excessive.

That doesn't mean that in this particular situation they may not have had the effect of inducing bradycardia, but I think they were appropriate doses and used in an appropriate situation. And the post mortem propanolol blood level that was done indicated too a therapeutic concentration of propanolol existed in this patient.

Q. Doctor, can I refer you to that level specifically if you would. I refer you to Mr. Cimbura's reports dated January 11, 1982. That is Exhibit 95A, Mr. Commissioner.

A. Is there a page number? Which one?

Q. January 11, the first one, Dr. Kauffman, at page 2.

Do you have that, Doctor?

A. Yes.

Q. I refer you, Doctor, specifically to Item T-22 the third from the bottom.

A. Yes.

Q. Which indicates that a sample of blood like fluid which was reported to be chest fluid was found to contain 0.007 milligrams per cent of Inderal. Do you see that, Doctor?

A. Yes.

Q. Were you aware of that finding by Mr. Cimbura, Doctor, at the time you prepared your first reporting letter to Mr. Wiley?

A. Not at the time of the first reporting letter. I was aware when I wrote my subsequent amendment to the report.

Q. As I understand it, Doctor,

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you did specifically address the issue of that level in your second report to Mr. Wiley?

A. Yes, I did.

Q. Could I ask you now to refer to the first page of your second reporting letter.

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Do you have that, doctor?

A. Yes.

Q. Doctor, in the first paragraph under the discussion concerning Justin Cook, you indicate as follows -- I'm sorry, you first indicate the concentration of propranolol which was measured in post mortem blood and you quote the level of .007 mg. per cent that you have just referred to in Mr. Cimbura's report. You then indicate:

"I did not specifically comment on the concentration of propranolol in my original report and the question was raised as to whether or not this concentration was consistent with the doses of propranolol the patient was reported to have received prior to his death. The concentration of 0.007 mg. per cent is well within the range of concentrations reported in patients receiving therapeutic doses of propranolol and is consistent with the propranolol administered to the infant prior to his death."

Once again, doctor, when you express the opinion that that concentration of

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propranolol was consistent with the doses which the infant was recorded to have received during life, were you addressing your mind to all the doses of Inderal which were prescribed in the 18-hour period prior to death as we have looked at them?

A. Yes.

Q. Is it also consistent, doctor, in your view with only two doses; that is, two doses of Inderal that were prescribed and administered as you suggested by the progress notes at 3:45 in the morning?

A. As you can see, the range of concentrations of propranolol measured in people receiving it is so wide, I thought it could be consistent with all the doses or simply the two that had been administered shortly before his death.

Q. To put the question perhaps a different way, doctor, assuming for the moment that the two doses of Inderal which are recorded to have been given at 3:45 in the morning or thereabouts were not given to the child, would that concentration as found in that post mortem specimen be consistent with the earlier dose of Inderal administered at midnight?

A. I think it could be.

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Q. So I take it then, doctor, that that concentration does not particularly assist us one way or the other in determining how many of all of those doses of Inderal were given to the child if indeed all of them were?

A. No. I don't think I can deduce that from the concentration itself, no.

Q. Doctor, does the opinion which you express concerning that concentration -- I am sorry, would the opinion that you expressed concerning that concentration be affected in any way if the concentration was measured not in post mortem blood, as you have recorded in your second reporting letter, but rather in chest fluid, as appears to be suggested by Mr. Cimbura's report?

A. I don't really know because I have absolutely no information as to what happens to propranolol post mortem and in different fluids after death. I really can't answer that with any knowledge.

Q. Thank you, doctor.

Doctor, there has been evidence before the Commission suggesting that a medication error might have occurred with Justin Cook, such that digoxin might have been mistaken for Inderal and,

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either inadvertently or deliberately, been administered to Justin Cook just prior to his Code 25 being called.

Did you, doctor, in assessing this case, take into account the possibility that such a medication error might have occurred?

A. I took it into consideration and thought about it. I couldn't really, from the information I had, see that that was a very likely probability and, so, I didn't develop it or consider it further.

Q. Doctor, could I refer you to page 2 of your second reporting letter.

A. Just a second.

Q. The first paragraph and the last sentence of that paragraph reads, doctor, as follows:

> "The propranolol concentration in post mortem serum is consistent with the assumption that he did receive the doses of propranolol recorded in the chart and it is unlikely that digoxin was substituted for propranolol in those instances."

I take it, doctor, that at the time you delivered this letter to Mr. Wiley that was your

II5 opinion?

A. That was, yes.

I was talking about likelihood and so, that was my opinion and I think it still is, that it was unlikely. I didn't think that the levels could totally answer that question, but I thought it was unlikely.

Q. By levels, are you referring to the concentration of propranolol that was measured?

A. Right.

Q. Apart from the level itself, doctor, if there was anything else upon which you based that opinion, would you elaborate on that for us, please.

A. Well, I am not sure how broadly to answer that question. I was taking a number of things into consideration, including what I was aware of; changes that had taken place in the Hospital in terms of the dispensing of digoxin shortly prior to Justin Cook's death. I was taking into consideration the time that he had received medications prior to his death, particularly by the intravenous route. I was taking into consideration the volume, the amount of digoxin that could have been delivered by that particular route and those two doses - could have

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been digoxin instead of pro[illegible]
seem to me that the amount
been delivered in that volume;
I thought it highly unlikely that that qu[illegible]
digoxin, even if it was the adult intravenous preparation, would produce the kind of serum and tissue concentrations that he had.

Q. Doctor, may I stop you there for a moment then.

Dealing specifically with the two doses of Inderal that are recorded as having been administered between 3:45 and 3:55, we know the recorded aggregate of those two doses was .6 millilitres. Are you saying that it is your opinion that were .6 millilitres of digoxin to have been mistaken for that amount of Inderal, that would not account for the levels found both in the ante mortem and post mortem serum of Justin Cook?

A. I think it is somewhat unlikely. I would have to do the arithmetic again but, as I recall doing the arithmetic of the amount of digoxin and the assumptions I had made about how much it would take to produce particular concentrations, assuming the things that I had outlined in my report, it was unlikely that this dose would, given at that

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point in time, produce those concentrations, particularly the tissue concentrations.

Q. That was my next question, doctor; whether or not that amount of digoxin administered at that time could account for the levels that we have seen in the fresh tissue specimens of Justin Cook.

A. Highly unlikely that it would.

Q. Doctor, may we address the same issue, please, with respect to the dose of Inderal that was administered at 12 midnight.

You recall that that dose was, according to the medication record, given orally in the amount of .4 -- well, it may in fact be 4 mg, doctor. I am not sure if that is a decimal mark or not.

A. What page is this?

Q. Page 17 of the medication sheet.

A. Let me look at that. I think it was 4 mg.

Yes, propranolol, 4 mg. orally every six hours. He had been switched to that higher dose earlier.

Q. Doctor, may I ask you

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similarly, with respect to that dose, if 4 mg. of digoxin had been administered orally at 12 midnight in substitution for the Inderal which was intended, could that amount have produced, in your opinion, the digoxin levels found in the serum and fresh tissue of this child?

A. I don't think we can assume. You can't extrapolate 4 mg. of propranolol from 4 mg. of digoxin. You would have to look at the volume at which that propranolol was administered and translate that into the volume of digoxin preparation, and I am not sure what oral propranolol preparation is being used that would administer those doses.

Q. I can't help you at the moment, doctor, about the forms in which propranolol was available at the time.

A. You see, the problem is, as far as I am aware, there was no oral propranolol preparation, no liquid propranolol preparation available, but I may be wrong because I am not familiar with the Canadian products. If it was the intravenous propranolol liquid, that would, I believe, contain 4 millilitres. So that if, instead of the 4 millilitres of propranolol given orally, one gave 4 millilitres of a liquid digoxin preparation, then we could calculate the number of milligrams of digoxin

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that it would be. Then we have to assumewhich liquid digoxin preparation might have been used.

Q. Doctor, to assist you with that, I will speak to my friends again at the end of the day and I may be able to have that information for you tomorrow to permit you to do that.

A. Then we can do the arithmetic and say what the possibilities could have been.

Q. Thank you, doctor.

I take it, however, doctor, that apart from the forms in which Inderal is available on these wards -- I should ask you, are you familiar with the forms in which digoxin was available on these wards during the period in question?

A. Yes, I am. I was provided that information.

Q. Doctor, accepting the view that you have expressed in your report for the moment that digoxin was administered during life to this child, I take it that as part of your review of Justin Cook, you did attempt to estimate how large a dose might have been administered, by what route and what the likely timing of the administration was.

May we deal first with the question of the amounts.

I110

As I understand it from the contents of your first reporting letter to Mr. Wiley, making such assumptions, you have attempted to estimate both a minimum amount and a maximum amount that might have been administered to achieve those levels. Do I have it correctly?

A. That is correct.

Q. Could we deal first with the question of the minimum amount, doctor. Could you explain to us what you estimated that amount to be and the basis for your calculation?

A. I estimated, based on my assumptions, I estimated that this would have been approximately half a milligram of digoxin. You have to remember that this kind of exercise carries a great degree of uncertainty with it because we are making assumptions that we have no way of proving of disproving but, if you are willing to accept those assumptions, then we can make some estimates. I think it is terribly important for everybody to understand that these assumptions may or may not be accurate and the estimates then have a great deal of inherent variability.

Q. Leaving aside for the moment, doctor, the assumptions that you made - and we will

IIl1

return to those - you have told us that in your estimation the minimum amount necessary to account for those levels would be half a milligram?

A. Yes.

Q. And referring now, doctor, to the first full paragraph on page 4 of your reporting letter, I take it that your estimate was that that amount would require a volume of the intravenous pediatric preparation of approximately 10 millilitres?

A. That is correct.

Q. And similarly, reading from the same paragraph, that it would require a volume of the IV adult preparation of approximately 2 millilitres?

A. That is correct.

Q. Do I have that correctly, doctor?

A. Yes.

Q. Doctor, bearing in mind the forms in which digoxin was available on these wards, both in the adult and pediatric injectable and intravenous forms, can you help us as to how much of the pediatric preparation we are talking about based on that volume and that approximation of amount?

A. How much in terms of...?

Q. Vials.

II12

A. Vials. The adult injectable was supplied in 2 millilitre volumes, so that would be equivalent to one vial of the adult preparation.

BmB.jc
JJ

The paediatric injectable was supplied in 0.05 milligrams per millilitre in 1-millilitre vials, so, that would be 10 vials. These are approximations, I wouldn't quibble with a little bit on either side.

Q. Doctor, there is, as well, as I understand it, when I suggested to you that the volume for the intravenous paediatric preparation as stated in your report would be 10 millilitres, I take it that that is a number that we find in your second report as the number which appears on page 4 as 5 millilitres?

A. That is correct, I had to amend that because when I wrote my report I was assuming concentrations that are supplied in the United States preparation and I was incorrect. I found out later that the Canadian paediatric preparation is one-half the concentration that the U.S. preparation is. So, that is the reason for the discrepancy.

Q. All right. I take it, Doctor, when you learned of the difference in the two preparations between the United States and here you recalculated the volume necessary and supplied that information to Mr. Wiley?

A. That is correct, that is what is contained in the second letter, yes.

JJ.2

Q. And Doctor, as well, you have told us that you made a number of assumptions and you have immediately stated that they may or may not be accurate and if inaccurate that there is a great deal of variability that could result. Do I have that correctly?

A. That is correct.

Q. Could you outline for us please briefly the assumptions which you did make and the basis in your view for treating them as reasonable assumptions to make in this instance?

A. Okay. The only assumption I had that I felt any confidence in was the baby's weight because that was stated on the chart. To make an estimate of the amount of digoxin administered I had to make some assumption as to how long after the dose was administered the baby died, and that was an unknown. So, I assumed that in this particular estimate the death occurred within less than an hour, or maybe even shorter than an hour, any time less than an hour after injection. I assumed because of that that there was minimal distribution into the tissues from the central compartment and that there was no significant elimination of digoxin from the body during that period of time.

JJ.3

I also had to assume a volume of distribution of the central compartment, so, I went to the literature and I looked to see what had been reported as estimates of the central volume of distribution for digoxin in infants and, as I recall, the different studies have shown a range anywhere from .5 to .6 up to over 1. There was one study that specifically designated a central compartment volume of 1.3 and I used that then for my estimate.

But I must say that one could equally, with equal validity, do the same calculation assuming .6, .8, 1, whatever, somewhere in that range. I thought at the time this study gave me the best estimate, so, I used it.

And then with the equation that the dose equals the concentration times the volume of distribution times the volume weight I calculated the possible dose.

MR. STRATHY: I'm sorry, do you think I could just have that last weight again, please?

THE WITNESS: Let me get my notes and I will give it to you in detail. I see there isn't a blackboard here or I would write it out for you.

MR. YOUNG: Mr. Commissioner, there is a blackboard here.

JJ.4

THE COMMISSIONER: There is one at the back. Could we have the blackboard, please.

MS. CRONK: Would it be of assistance for you, Doctor, to have the blackboard?

THE WITNESS: It might be of assistance to the people who are interested if I would just put it upon the board for them.

THE COMMISSIONER: Yes, all right.

THE WITNESS: I will give it to you verbally while we are waiting for the blackboard.

(2) The estimated dose was calculated from the concentration that I had, which I used the number 70 micrograms per litre, which is the same as 70 nanograms per millilitre. And that, multiplied by the volume distribution of the central compartment, which, as I said, I used 1.3 litres, multiplied times the baby's weight, which was 5.37 kilograms, and if you multiply all those numbers out you will come out with something very close to .5 milligrams.

MS. CRONK: I am sorry, I didn't hear the very last part?

THE WITNESS: I said if you multiplied those out you will come out with something very close to .5 milligrams.

MS. CRONK: Thank you.

JJ.5

THE WITNESS: A. On my notes I have it as .489.

Q. Thank you.

A. I'll put my assumption up and then the equation, okay.

I have changed the concentration to micrograms per litre to keep all the volume units the same, that's all I have done. So, the dose equals the concentration times the volume distribution times the body weight and if you assign these values to it, you will get 70 times 1.3 times 5.37 and if I did my arithmetic right, that is approximately .5 milligrams.

Q. Thank you, Doctor. Doctor, could we deal with the assumptions which you did make in this case one by one if we may. The birth weight is obvious enough, I take it that you drew that directly - the body weight, I'm sorry?

A. I used the body weight.

Q. That's right, I'm sorry.

A. That was on the chart.

Q. You drew that directly from the chart of the child?

A. Yes.

Q. As I understand it, Doctor, you assumed, for the purposes of this estimation as well

JJ.6

that a single IV bolus was the likely method of administration?

A. That's correct, that's correct.

Q. Can you help us, Doctor, as to why you preferred that assumption with respect to mode of administration?

A. I had no reason to believe that multiple doses of digoxin had been administered. I thought with the high concentration and the short time course of the terminal events that it was highly unlikely that the infant had received multiple doses of digoxin over a longer period of time or had received the dose hours and hours prior to the critical events. I thought it was most likely that if it was given it was given intravenously because the volumes required to give a liquid oral preparation would have been somewhat difficult in this child with his condition at the time and would have been much more difficult in giving it intravenously.

I thought it was highly unlikely, quite improbable that it was given slowly intravenously, such as putting it in the IV fluid or in the volutrol because that would have taken hours and hours to have administered it and probably would not have produced such high concentrations before the infant showed some

JJ.7

signs of toxicity. So, those were the things I took into consideration when I made that assumption.

Q. All right. Doctor, dealing first if we may with the possibility of oral administration and you have told us that you considered that to be unlikely, as I understood it?

A. Right.

Q. As I understand it, Doctor, you did however attempt an estimate as well as to the amount of oral elixir which could produce the serum concentrations in the tissue levels that we have seen in Justin Cook. Do I have that correct?

A. That is correct, I did do that.

Q. All right.

THE COMMISSIONER: Before we go on, isn't there a decimal problem somewhere in that equation because I just can't see it at all, 70 times 1.3 times 5.37 equals .5?

THE WITNESS: Well, your problem is that the 70 should be that. There is a decimal problem, yes.

THE COMMISSIONER: Oh, yes, all right.

MS. CRONK: Q. Doctor, dealing then for the moment with the question of administration by use of the oral elixir, can you tell us please

JJ.8

what you estimated would be the minimum amount necessary to achieve these levels if that mode had been used?

A. When I did I had to introduce another factor here and that was the fraction of the dose I estimated would be absorbed and from the literature we know that 70 to 80 per cent of the dose would be absorbed. So, I assumed 70 per cent for this purpose and assumed that it was absorbed fairly rapidly. I also assumed that death occurred five to six hours after the injection of the dose and if that were the case -- I'm sorry, this would take a volume -- I'm sorry, I first assumed that the infant died shortly after the dose, approximately an hour and under those conditions I estimated that it would require a volume of the paediatric elixir of approximately 14 millilitres, which would be approximately one-half ounce.

Q. All right. Well, Doctor, to stop there for a moment because my purpose is to understand the assumptions which you made in calculating the minimum amount of the dose for an IV rapid single dose bolus administration and you have told us for the moment then I take it that based on your estimations you felt oral administration could be ruled out?

JJ.9

A. I thought it was highly unlikely simply because of the feasibility of giving that much volume to a baby that was this sick at that point in time.

Q. All right, and I will come back then, Doctor, to the actual calculations that you did on that basis in a moment.

But dealing again with the minimum dose calculation which you made for a rapid single bolus IV administration, you have told us that you have used a volume of distribution based, I think you told us on your review of the literature, of 1.3 litres per kilogram.

We have heard in evidence, I tell you, Dr. Kauffman, from Dr. Spielberg, his view that the central volume of distribution of digoxin varies from .6 to .1 litres per kilogram. Can you help me, Doctor, specifically as to how you arrived at the 1.3 litres per kilogram as opposed to a ---

MR. STRATHY: Excuse me, I think it was .6 to 1, I don't think it was .6 to .1.

MS. CRONK: I'm sorry, did I say .1. You are quite right, .6 to 1.

THE WITNESS: Let me see, I may have in my notes the reference to that because I did jot

JJ.10

it down, tried to tabulate the estimates.

MS. CRONK: Q. Thank you, Doctor.

A. There is a paper that I have noted here and Air Canada have my reprints some place between here and Newfoundland right now.

Q. I see, together with your estimates.

A. Together with my toothbrush.

Q. Well, one would be of more assistance than the other.

A. But I can tell you the date of the reprint from my notes and the first author and maybe we can find it later on if anybody wants to look at these. This is a paper by Warburton from 1980 who reported a volume distribution alpha of 1.33, Wettrill in 1976 reported a volume distribution alpha of 1.31, Hastreiter .62 and he called it volume distribution central. There are steady state volumes distribution or volume distribution beta, that is after distribution. So, those were the numbers that I used. So, I would say the range is .6 to 1.3 approximately based on those papers.

Q. All right. So, for the purposes of these calculations, Doctor, and having regard to the literature which you reviewed, you used a volume

JJ.11

of distribution for the central volume of distribution at the higher end of the reported range in the literature?

A. Yes. The reason for doing that was because there were more papers that I had tabulated reporting that than reporting the lower volumes.

Q. All right.

A. So, I simply went with the preponderance of the reprints that I had at that time.

Q. Doctor, is the central volume of distribution of digoxin a matter which pharmacologically has in your view been clearly established?

A. We have data from numerous studies in which it has been estimated - I'm not sure that it has been totally clarified. I think there are a lot of questions yet as to what it means but I think we have a common understanding as to what it means conceptually.

KK/EMT/ak

I take it, Doctor, that if a lower central volume of distribution figure had been used in these calculations that would necessarily have directly impacted on the minimum amount of dose that you have calculated?

A. Yes, it would require a lower dose to estimate, and I've absolutely no qualm, no quibble with that.

As I said, I think these estimates are very - I don't know which word to use, but they contain a great deal of variation, variability, and I don't think we should get hung up on one number over another within that range.

I think we could estimate this dose with different reported volumes of distribution of the so-called central compartment and come up with a range of possible minimal doses and I would have no problem with any of those.

I think they are equally open to question or equally valid.

Q. And, Doctor, dealing with certain of the other assumptions that you made, as I understood you told us you assumed there was minimal distribution into the peripheral compartment, and I take it you were referring in that context to

KK2

the amount of distribution that had taken place during the alpha phase following administration of digoxin?

A. That is correct.

Q. Was that related as well, Doctor, to your assumption that death occurred within less than one hour following administration of the dose?

A. Yes, yes.

Q. Why, Doctor, in this calculation did you assume that time interval between administration and death?

A. Because I was estimating minimal dose, and during the early part of the alpha phase when minimal distribution had taken place would be the time that would require the least digoxin to produce that particular serum concentration.

As you get into the later alpha phase and blending into the - what is called the beta slope of the excretion curve, it takes increasingly larger amounts of digoxin to produce the same concentration in serum.

Q. Doctor, using the one hour time interval which you assumed in this case and

KK3

having regard to the concentrations of digoxin that were in fact reported in the fresh tissue specimens from Justin Cook, in your opinion if the dose of digoxin had been administered one hour prior to death could that account for the concentrations that were found in fresh tissue post mortem?

A. I think it could but I think it is less likely but I think it could.

We really don't have a handle on how rapidly the digoxin distributes into the tissues, and we also don't know the exact dose that he got. And without knowing those you can't answer that question with any certainty.

I think it is less likely that that was the case because of the high concentration in the myocardium as opposed to some time during partial distribution, so that there was time for some digoxin to get into the tissues and produce the high tissue concentrations, but still the distribution was not totally complete.

Q. Well, Doctor, may I understand that?

We have heard in evidence from Dr. Spielberg - his evidence, Mr. Commissioner, is found in Volume 54 at pages 2008 and 2009,

KK4

Dr. Kauffman, his opinion that with an intravenous administration of digoxin the alpha phase of distribution following the first few immediate minutes takes from 2½ to 4 hours after which a steady state of concentration is achieved.

Is that an estimation of the time period for distribution with which you would agree or disagree?

A. In general I would agree with it. It may be a little longer than that in some patients. The calculated alpha I guess you could call it half life, the calculated alpha exponent is somewhere between, if I remember right, 30 minutes and maybe a little over an hour and you would expect distribution then to be complete in approximately five of those half lives so that it could be I suppose anywhere from 2½ to 5 hours. Something in that range.

Q. Doctor --

A. I wouldn't quibble with those numbers because I don't think we know enough specifically to fight about that, but I would agree with that general range and because of that we usually advise people the time it takes to absorb an oral dose, we usually advise them to wait at least six

hours before getting a serum concentration in a clinical setting.

Q. Doctor, when you said that you considered it unlikely that a dose administered at one hour prior to death could account for those levels, and I believe you said you felt it could but it was unlikely and you felt more likely it had been administered in time to permit partial distribution, were you suggesting from that the dose in your view was likely administered longer than one hour prior to the child's death?

A. That would be my estimate.

I think it is somewhat unlikely that you would see that high tissue concentration shortly - in that short a time, 30 minutes to an hour.

With a large enough dose you could see that they could, but I think it is more likely that it probably was administered several hours, and it is hard to say much more specifically than that.

I doubt if distribution totally took place because I think it would be difficult for the patient to survive with that high concentration for very long so we are limited on the other extreme by those constraints, and so based on that I would

K6

suspect that the dose was administered some time between 1 to 2, 1 to 3 hours, something like that.

Q. Prior to death?

A. Prior to death, yes.

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KK2-1

Q. We know, Doctor, in this context as I told you that the child began to experience difficulties at approximately 3:45 in the morning.

MR. STRATHY: Excuse me. I have enough trouble understanding evidence that is being given, and I just was not clear when the doctor was talking about likely that the dose was administered more than an hour prior to death. Is he talking at this point about the oral administration hypothesis or is he talking about the ampoule administration?

THE WITNESS: You mean the oral versus the IV?

MR. STRATHY: Yes. If I may, Mr. Commissioner?

THE COMMISSIONER: I thought you had come down in favour of the IV?

THE WITNESS: I had calculated - I had estimated a possible oral dose but I had discarded that essentially and my comments now were assuming an intravenous dose.

MR. STRATHY: Thank you.

MS. CRONK: Q. Doctor, you have told us that your best judgment on the matter is that that intravenous dose was likely to have been administered

KK2-2

some time between one and two and three hours prior to the child's death. Do I have that correctly?

Q. All right. Doctor, we know from the medical record of the child that he began to experience difficulties at approximately 3:45 in the morning. The doses of Inderal that we discussed a few moments ago are recorded as having been administered between 3:45 and approximately 4:10 in the morning, and a Code 25 was called at 4:20. The child ultimately was pronounced dead at 4:56 in the morning.

When you say, Doctor, that in your judgment the dose was administered one to three hours prior to death, what time are you addressing when you make that calculation?

THE COMMISSIONER: The time of his death.

THE WITNESS: That is I suppose in many ways a difficult question. He was actually pronounced dead around as you say was at 4:55?

MS. CRONK: Q. 4:56.

A. Death doesn't always occur simultaneously and instantaneously.

What I think I intended and should have said was that it may have been given in that time

KK2-3

frame prior to obtaining the sample which was obtained somewhere during that 30, 45 minute period.

Q. You are referring, Doctor, now to the sample obtained during the resuscitation effort?

A. Right.

Q. Doctor, you have indicated as well that apart from estimating the minimum dose which might have been administered to the child intravenously to account for these levels, you as well attempted to estimate the maximum amount of dose.

Would you explain for us, Doctor, what your estimate was as to the maximum amount of the dose and the basis on which you arrived at that calculation?

A. I estimated that it would take approximately 4 milligrams. I wrote down 4.3 milligrams. I don't think we can quibble about decimal points in this area, but it was approximately 4 milligrams would produce such a serum concentration. Again the number that you come out with is highly dependent on which assumptions you make.

Q. Well, Doctor, leaving aside your assumptions for a moment and recognizing that your estimated maximum dose was 4.3 milligrams, as I read your report you suggested that that would require a volume of the paediatric injectable preparation of 86 millilitres?

KK2-4

A. That is correct.

Q. And do I correctly take from that, Doctor, given the volumes in which we know that form of digoxin was available on these wards, that would require 86 paediatric ampoules?

A. That is right.

Q. And, Doctor, do I read your report correctly as well that with a dose in that amount it is your view that that would require a volume of the adult intravenous injectable preparation with a volume of 17.3 millilitres?

A. That is correct.

Q. And again, Doctor, can you approximate for us or relate that to the number of adult vials that would be required to administer a dose in that amount?

A. I think the paediatric preparation, the milligrams and millilitres are the same so it would be - well in terms of vials it would 86 vials.

Q. I am sorry, I was talking now about the adult.

A. Oh, the adult. The half of 17, 8-1/2, 9 vials.

Q. Doctor, you have alerted us once again to arrive at that estimation you made a

KK2-5

number of assumptions. Could you outline very briefly for us the assumptions that you made and the basis upon which you made them?

A. Okay. Let me if I may refer to my notes again.

I assume that the drug was totally distributed and again that it was given as a single intravenous dose; 100% of it was infused; because distribution had to take place death had occurred at least five hours after the dose or the dose was administered at least five hours prior to obtaining a sample; that there was distribution equilibrium with a peripheral compartment which includes tissues and that the elimination half life was around 30 hours and that the time of death occurred or the time the sample was obtained was approximately - I had to put a specific number in the equation so I assumed a specific time interval of six hours between the dose and the time of obtaining the sample.

And I assumed again a weight, the same weight of course. A volume of distribution of the beta volume distribution and I chose a middle ground for this. These estimates range anywhere from 5 to 6 litres per kilo up to 15 or 16 litres per kilo. I chose 10 as a mid point. I had no reason to pick

either extreme so I picked 10 litres per kilo, but as you can see one could legitimately pick either extreme or anywhere in between and come up with somewhat different numbers.

I had to plug a rate of elimination or an elimination rate constant into the equation so I assumed a half life of 30 hours. That gives us an elimination rate constant of 0231 hours, reciprocal hours, and the time interval as I told you was six hours.

Then the equation is a little more complex here because you have to build into it - you have to account for the amount of drug that is eliminated from the body during the time interval as well so the equation looks a little different, but it really isn't that much different.

The volume of distribution times the body weight times the concentration divided by the elimination, that is - if anybody wants to get into this it is okay but just take my word for it. It is e to the minus K.

Now this factor here accounts for how much drug left the body during that six hour period, and if you do that and plug in these numbers to all that you come out with about 4 milligrams, and this 70 again is 0.07 when you put it into milligrams.

MS. CRONK: Doctor, I think speaking clearly for myself that that is quite enough for me to ingest over the evening and I propose, Mr. Commissioner, we break at this time.

THE COMMISSIONER: All right. Ten o'clock?

MS. CRONK: Yes.

Thank you, Doctor.

--- Whereupon the hearing was adjourned at 5:00 p.m. until Tuesday, November 29th, 1983 at 10:00 a.m.